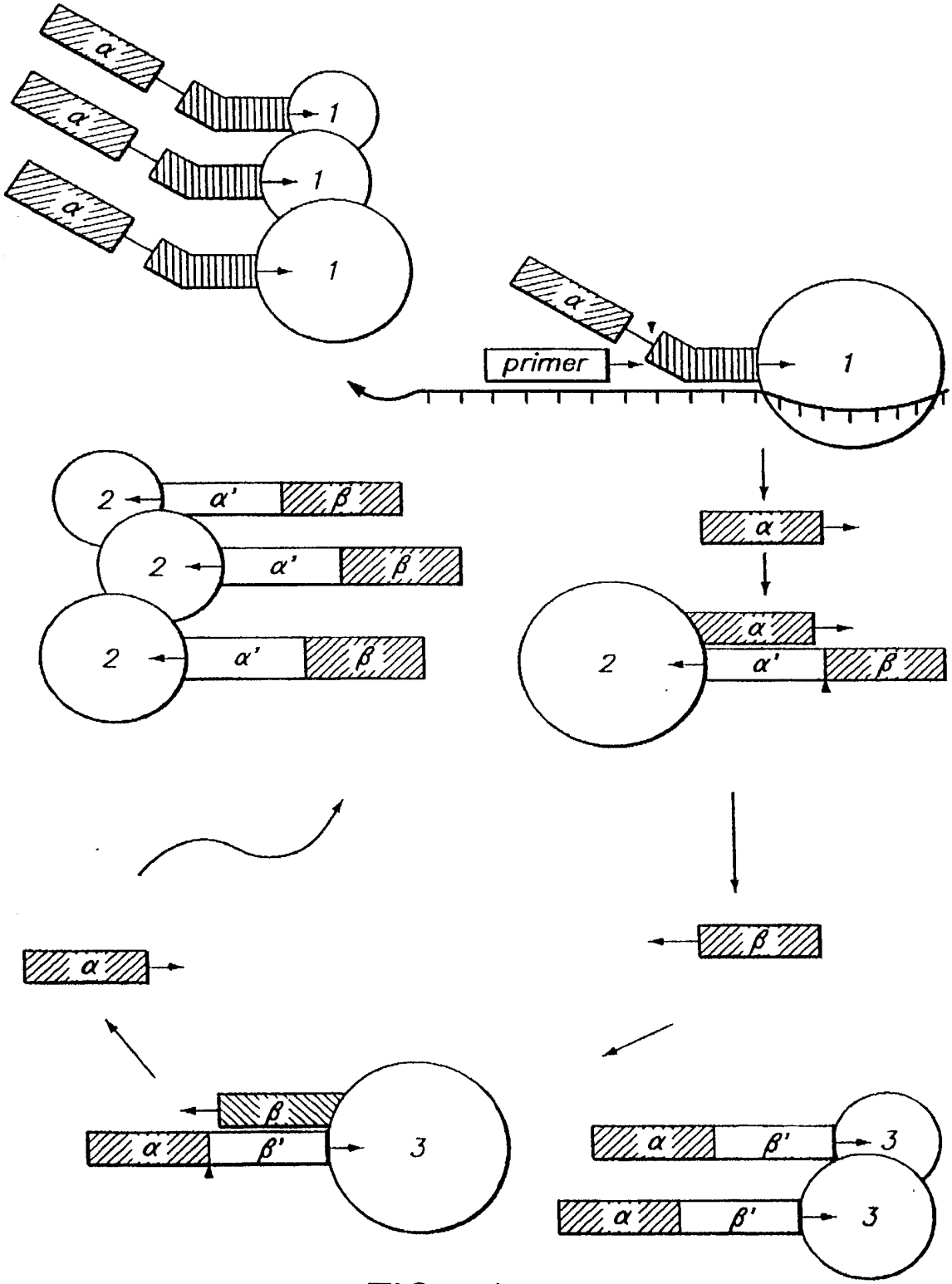


FIG. 1A

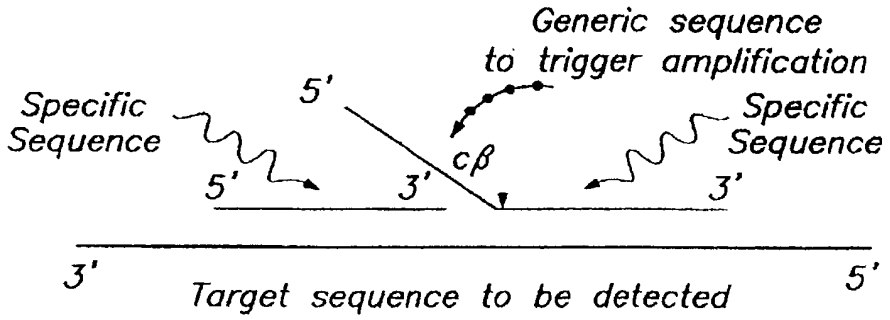


FIG. 1B PART ONE: TRIGGER REACTION

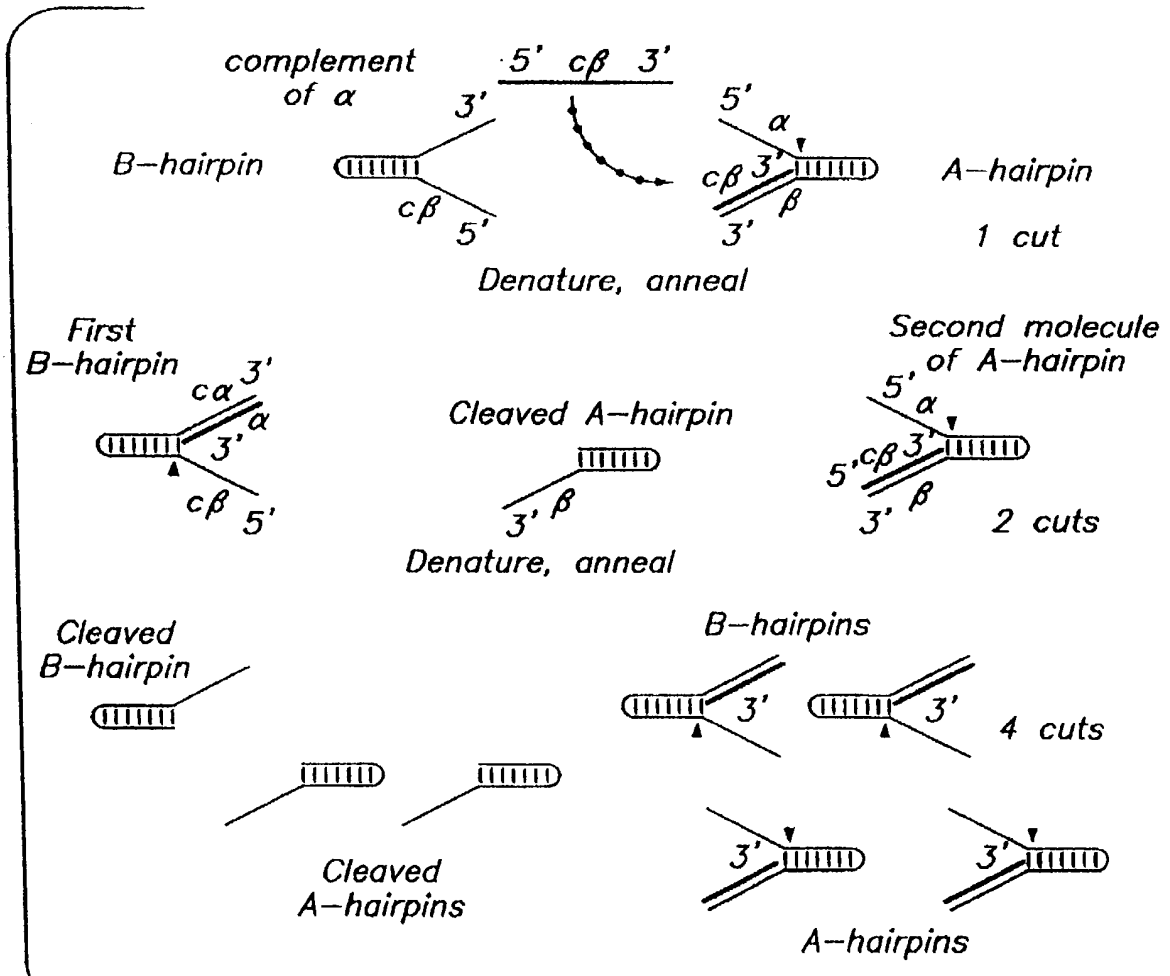


FIG. 1C PART TWO: DETECTION REACTION

FIG. 2A

```
MAJORITY [SEQ ID NO:7]  ATGXXGGCGATGCTTCCCCTCTTTGAGCCCAAAGGCCGGGTCCTCCTGGTGGACGGCCACCACCTGGCCT

DNAPTAQ  [SEQ ID NO:1]  ...AG..G......G................G......................................  70
DNAPTFL  [SEQ ID NO:2]  .......................................C..G............................  67
DNAPTTH  [SEQ ID NO:3]  ...GA...........G........A............................................  70

MAJORITY                ACCGCACCTTCTTCGCCCTGAAGGGCCTCACCACCAGCCGGGGCGAACCGGTGCAGGCGGTCTACGGCTT

DNAPTAQ                 ...........CA...........................G..G..........................  140
DNAPTFL                 .............T.....C...................C........C..T..................  137
DNAPTTH                 ................................G.....................................  140

MAJORITY                CGCCAAGAGCCTCCTCAAGGCCCTGAAGGAGGACGGGGACXXGGCGGTGXTCGTGGTCTTTGACGCCAAG

DNAPTAQ                 .......................C...............-.......A......................  207
DNAPTFL                 ......A...........................GT..T..............................  204
DNAPTTH                 ..................................T..AA...C..CT.......................  210

MAJORITY                GCCCCCTCCTTCCGCCACGAGGCCTACGAGGCCTACAAGGCGGGCCGGGCCCCCACCCCGGAGGACTTTC

DNAPTAQ                 ..........................G..GG.........................G.............  277
DNAPTFL                 ......................................................................  274
DNAPTTH                 .............................................GA......G.....C........C.  280

MAJORITY                CCGGGCAGCTCGCCCTCATCAAGGAGCTGGTGGACCTCCTGGGGCTTGCGCGCCTCGAGGTCCCCGGCTA

DNAPTAQ                 .......A.................................G.................G.....  347
DNAPTFL                 ..........G...............T............A..C...T...G..G.....T.......T  344
DNAPTTH                 ...........................................T..A.C.....................  350
```

FIG. 2B

```
MAJORITY [SEQ ID NO:7] CGAGGCGGACGACGTXCTGGCCACCCTGGCCAAGAAGGCGGAAAAGGAGGGGTACGAGGTGCGCATCCTC

DNAPTAQ  [SEQ ID NO:1] ..............C.......G.............................C.......C.........  417
DNAPTFL  [SEQ ID NO:2] T.............G.................CG.....................................  414
DNAPTTR  [SEQ ID NO:3] ..............T..C.....................................................  420

MAJORITY ACCGCCGACCGCGACCTCTACCAGCTCCTTTCCGACCGCATCGGCGTCCTCCACCCCGAGGGGTACCTCA

DNAPTAQ  .........AAA.....T.........................CA.............................  487
DNAPTFL  ..T.............................G..G.........A..........T...........G.  484
DNAPTTR  ........................A...G.C.........G.....................CC......  490

MAJORITY TCACCCCGGCGTGGCTTTGGGAGAAGTACGGCCTGAGGCCGGAGCAGTGGGTGGACTACCGGGCCCTGGC

DNAPTAQ  ..........C..........A.................C..C.......CC...............A.  557
DNAPTFL  ..................AC..............C.C.................................  554
DNAPTTR  .........A.........................C.....................T...C.....C.T  560

MAJORITY GGGGGACCCCTCCGACAACCTCCCCGGGGTCAAGGGCATCGGGGAGAAGACCGCCCXGAAGCTCCTCXAG

DNAPTAQ  C......GAG...........T.............................G..GAG......T..GG..  627
DNAPTFL  ............G..T...A.........G.....................A..G....A..CGC  624
DNAPTTR  ..................................................TC.........A..  630

MAJORITY GAGTGGGGGAGCCTGGAAAACCTCCTCAAGAACCTGGACCGGGTGAAGCCCGC···CXTCCGGGAGAAGA

DNAPTAQ  ..................GC.....................C.............A.............  694
DNAPTFL  .......................T..C..C.........A..........T.···.T.G.........C  691
DNAPTTR  ........A.....................................A.....A.AAAA.G.........  700
```

FIG. 2C

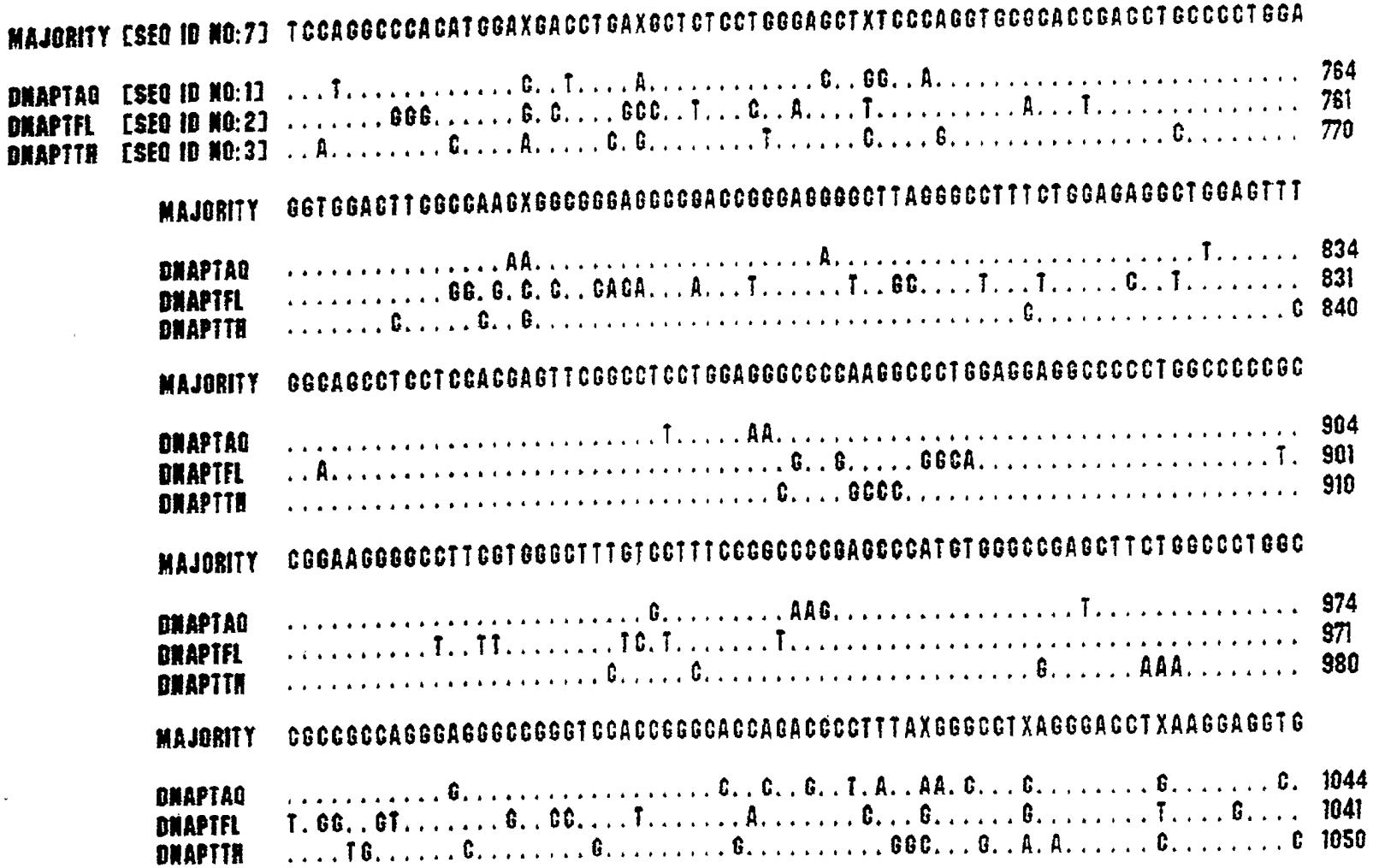

MAJORITY [SEQ ID NO:7] TCCAGGCCCACATGGAXGACCTGAXGCTCTCCTGGGAGCTXTCCCAGGTGCGCACCGACCTGCCCCTGGA
DNAPTAQ [SEQ ID NO:1] ...T.....G..T....A.....G..GG..A..... 764
DNAPTFL [SEQ ID NO:2] .....GGG.....G.C....GCC..T...C..A....T.....A...T..... 761
DNAPTTH [SEQ ID NO:3] ..A.....C....A.....C.G.....T.....C....G.....C..... 770
MAJORITY GGTGGAGTTGGCCAAGXGGCGGGAGGCCGACCGGGAGGGGCTTAGGGCCTTTCTGGAGAGGCTGGAGTTT
DNAPTAQ .....AA.....A.....T..... 834
DNAPTFL .....GG.G.C.C..CACA...A...T.....T..GC....T...T.....C..T..... 831
DNAPTTH .....C.....C..G.....G.....C 840
MAJORITY GGCAGCCTCCTCGACGAGTTCGGCCTCCTGGAGGGCCCCAAGGCCCTGGAGGAGGCCCCCTGGCCCCCGC
DNAPTAQ .....T.....AA..... 904
DNAPTFL ..A.....G..G.....GGCA.....T. 901
DNAPTTH .....C....GCCC..... 910
MAJORITY CGGAAGGGGCCTTCGTGGGCTTTGTCCTTTCCGGCCCGAGCCCATGTGGGCCGAGCTTCTGGCCCTGGC
DNAPTAQ .....G.....AAG.....T..... 974
DNAPTFL .....T..TT.....TC.T.....T..... 971
DNAPTTH .....C.....C.....G.....AAA..... 980
MAJORITY CGCCGCCAGGGAGGGCCGGGTCCACCGGGCACCAGACCCCTTTAXGGGCCTXAGGGACCTXAAGGAGGTG
DNAPTAQ .....G.....C..C..G..T.A..AA.C...C.....G.....C. 1044
DNAPTFL T.GG..GT.....G..CC....T.....A.....C...G.....G.....T....G.... 1041
DNAPTTH ....TG.....C.....G.....G.....GGC...G..A.A.....C.....C 1050

FIG. 2D

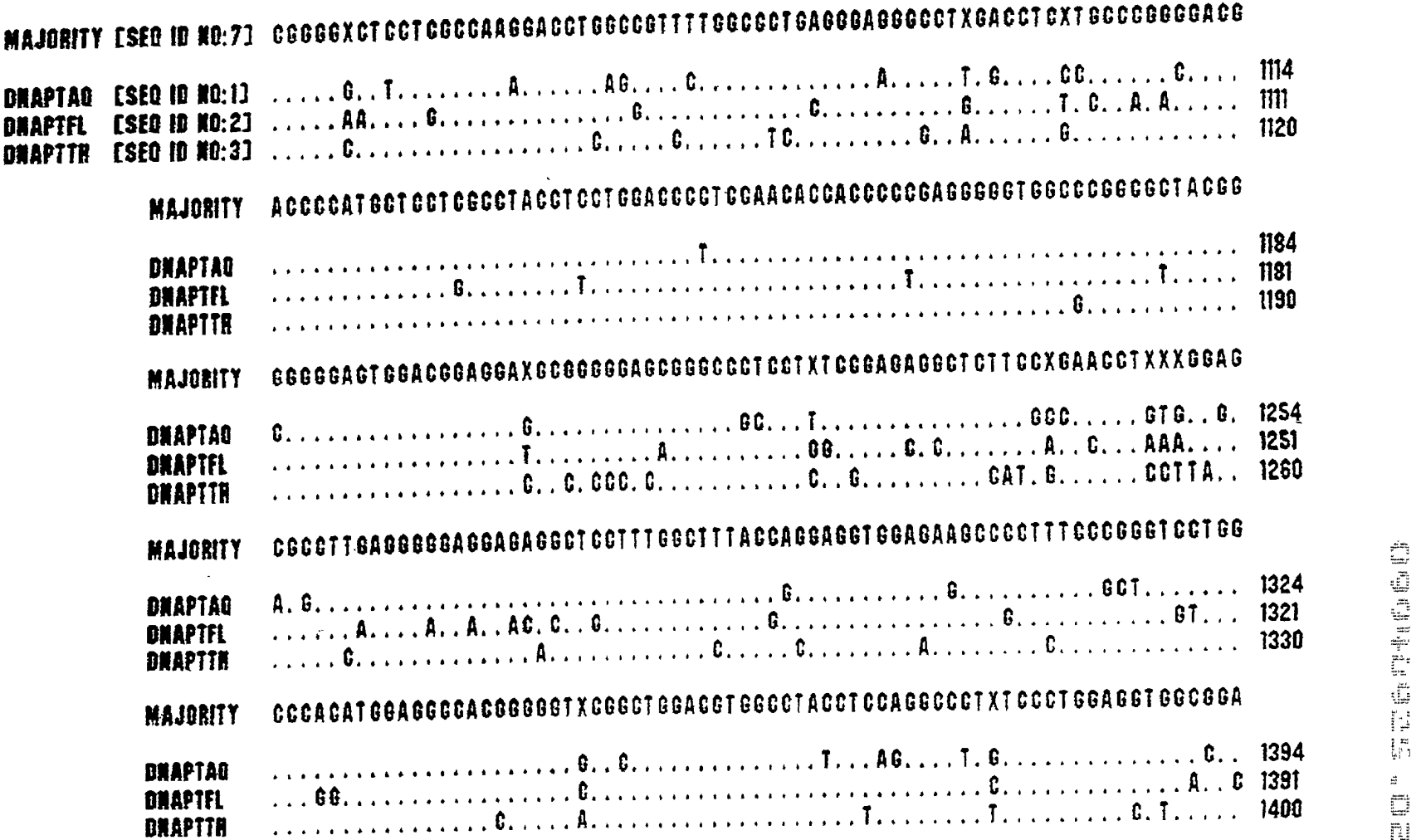

MAJORITY [SEQ ID NO:7] GGGGGXCTCCTCGCCAAGGACCTGGCCGTTTTGGCGCTGAGGGAGGGCCTXGACCTCXTGCCCGGGGACG
DNAPTAQ [SEQ ID NO:1] .....G..T.....A.....AG....C.....A.....T.G....CC.....C.... 1114
DNAPTFL [SEQ ID NO:2] .....AA....G.....G.....C.....G.....T.C..A.A..... 1111
DNAPTTR [SEQ ID NO:3] .....C.....C.....C.....TC.....G..A.....G..... 1120
MAJORITY ACCCCATGCTCCTCGCCTACCTCCTGGACCCCTCGAACACCACCCCCGAGGGGGTGGCCCGGGGCTACGG
DNAPTAQ .....T..... 1184
DNAPTFL .....G.....T.....T.....T..... 1181
DNAPTTR .....G..... 1190
MAJORITY GGGGGAGTGGACGGAGGAXGCGGGGGGAGCGGGCCCTCCTXTCGGAGAGGCTCTTCCXGAACCTXXXGGAG
DNAPTAQ C.....G.....GC...T.....GCC.....GTG..G. 1254
DNAPTFL .....T.....A.....GG....C.C.....A..C...AAA.... 1251
DNAPTTR .....C..C.CCC.C.....C..G.....CAT.G.....CCTTA.. 1260
MAJORITY CGCCTTGAGGGGGAGGAGAGGCTCCTTTGGCTTTACCAGGAGGTGGAGAAGCCCCTTTCCCGGGTCCTGG
DNAPTAQ A.G.....G.....G.....GCT..... 1324
DNAPTFL .....A....A..A..AC.C..G.....G.....G.....GT... 1321
DNAPTTR .....C.....A.....C.....C.....A.....C..... 1330
MAJORITY CCCACATGGAGGGCACGGGGGTXCGGCTGGACGTGGCCTACCTCCAGGCCCTXTCCCTGGAGGTGGCGGA
DNAPTAQ .....G..C.....T...AG....T.G.....C.. 1394
DNAPTFL ...GG.....C.....C.....A..C 1391
DNAPTTR .....C.....A.....T.....T.....C.T..... 1400

FIG. 2E

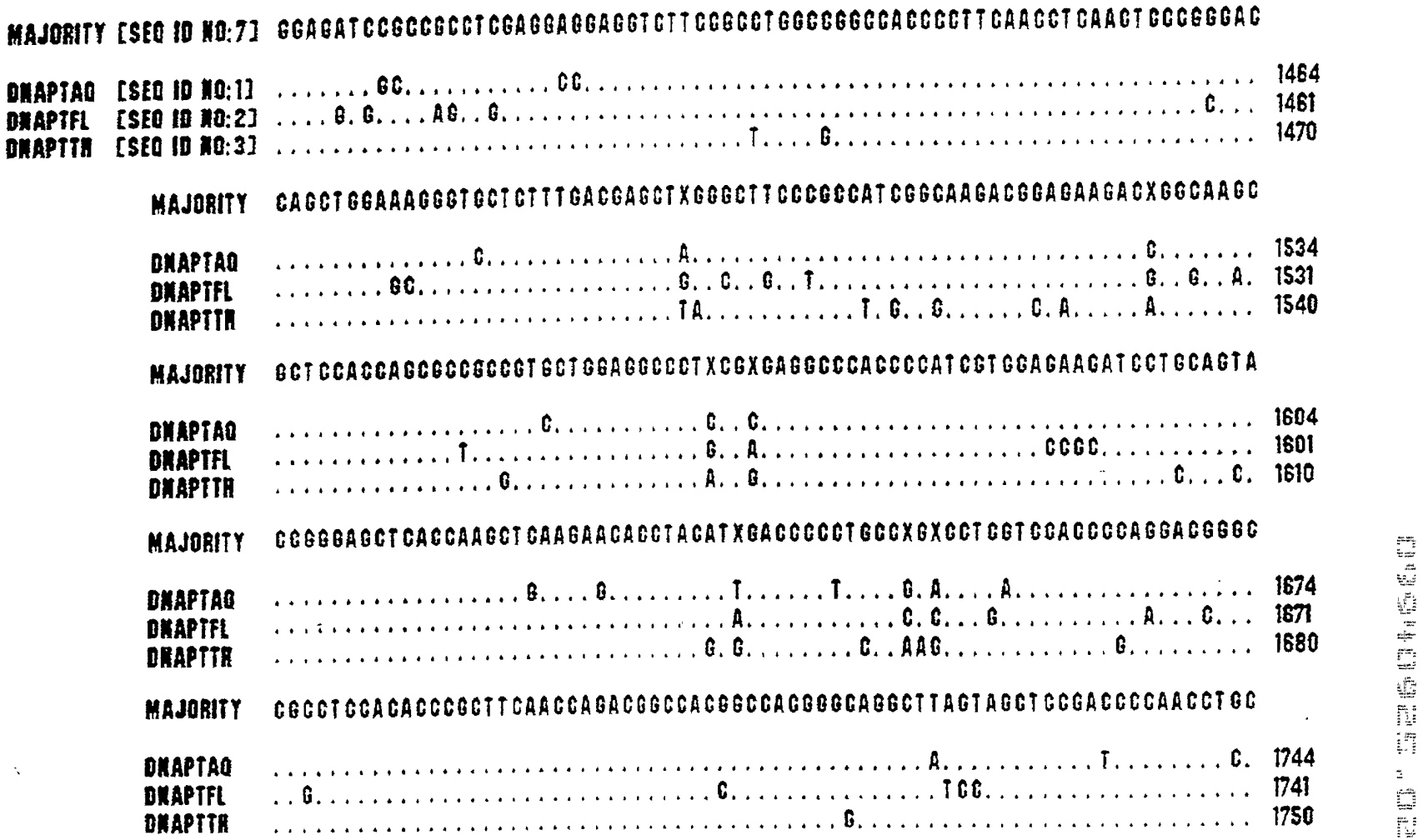

MAJORITY [SEQ ID NO:7] GGAGATCCGCCGCCTCGAGGAGGAGGTCTTCGGCCTGGCGGGGCACCCCTTCAACCTCAACTGCCGGGAC
DNAPTAQ [SEQ ID NO:1] 1464
DNAPTFL [SEQ ID NO:2] 1461
DNAPTTR [SEQ ID NO:3] 1470
MAJORITY CAGCTGGAAAGGGTGCTCTTTGACGAGCTXGGGCTTCCCGCCATCGGCAAGACGGAGAAGACXGGCAAGC
DNAPTAQ 1534
DNAPTFL 1531
DNAPTTR 1540
MAJORITY GCTCCACCAGCGCCGCCGTGCTGGAGGCCCTXCGXGAGGCCCACCCCATCGTGGAGAAGATCCTGCAGTA
DNAPTAQ 1604
DNAPTFL 1601
DNAPTTR 1610
MAJORITY CGGGGAGCTCACCAAGCTCAAGAACACCTACATXGACCCCCTGCCXGXCCTCGTCCACCCCAGGACGGGC
DNAPTAQ 1674
DNAPTFL 1671
DNAPTTR 1680
MAJORITY CGCCTCCACACCCGCTTCAACCAGACGGCCACGGCCACGGGCAGGCTTAGTAGCTCCGACCCCAACCTGC
DNAPTAQ 1744
DNAPTFL 1741
DNAPTTR 1750

FIG. 2F

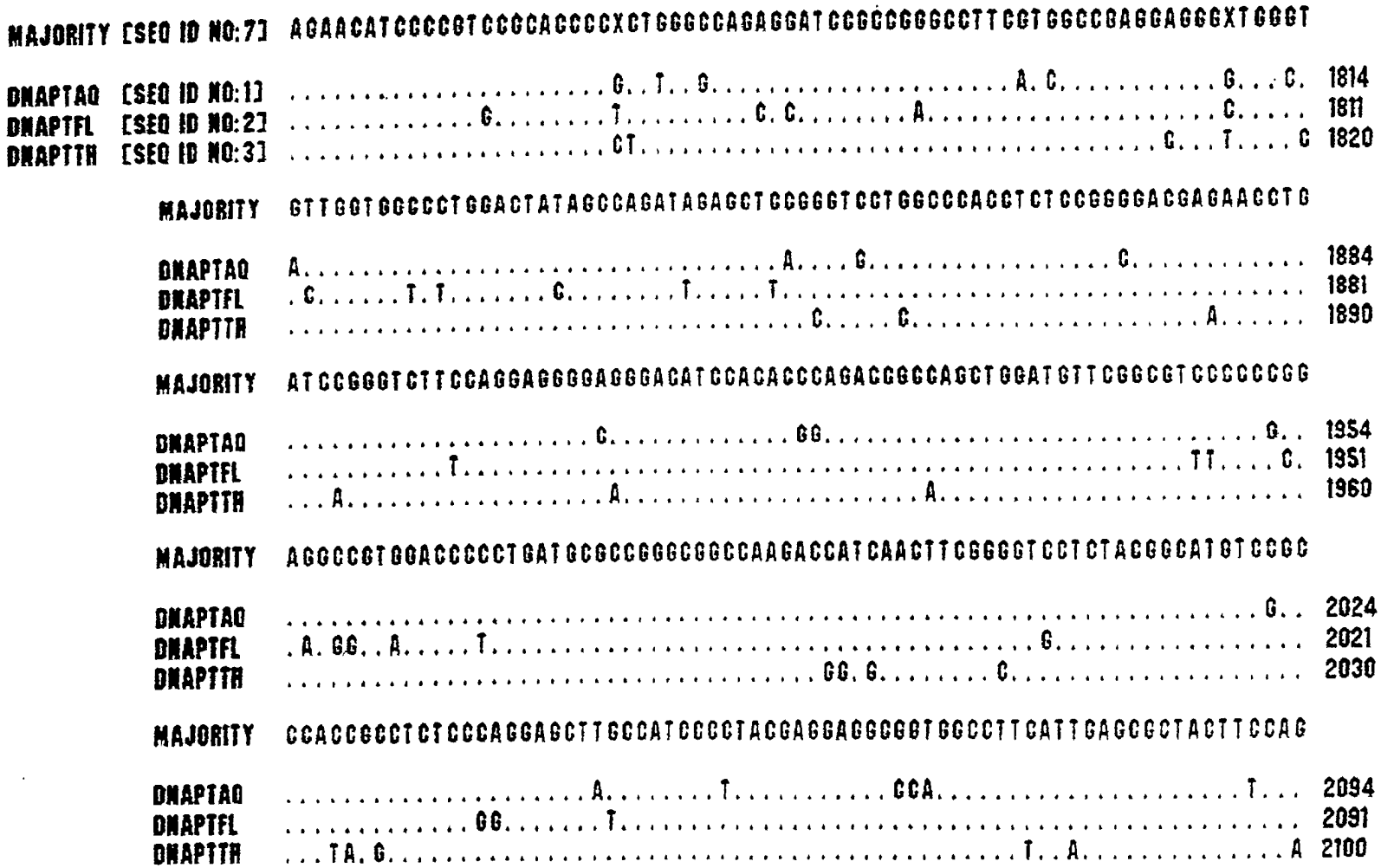

MAJORITY [SEQ ID NO:7] AGAACATCCCCGTCCCCACCCCXCTGGGCCAGAGGATCCGCCGGGCCTTCGTGGCCGAGGAGGGXTGGGT
DNAPTAQ [SEQ ID NO:1] ..........G..T..G..........A.C..........G...C. 1814
DNAPTFL [SEQ ID NO:2] ..........G.....T.....C.C.....A..........C..... 1811
DNAPTTH [SEQ ID NO:3] ..........CT..........G...T....C 1820
MAJORITY GTTGGTGGCCCTGGACTATAGCCAGATAGAGCTCCGGGTCCTGGCCCACCTCTCCGGGGACGAGAAGCTG
DNAPTAQ A..........A....G..........C..... 1884
DNAPTFL .C.....T.T.....C.....T....T..... 1881
DNAPTTH ..........C.....C..........A..... 1890
MAJORITY ATCCGGGTCTTCCAGGAGGGGAGGGACATCCACACCCAGACGGCCAGCTGGATGTTCGGCGTCCCCCCGG
DNAPTAQ ..........C.....GG..........G.. 1954
DNAPTFL ..........T..........TT....C. 1951
DNAPTTH ...A..........A..........A..... 1960
MAJORITY AGGCCGTGGACCCCCTGATGCGCCGGGCGGCCAAGACCATCAACTTCGGGGTCCTCTACGGCATGTCGGC
DNAPTAQ ....G.. 2024
DNAPTFL .A.GG..A....T..........G..... 2021
DNAPTTH ..........GG.G.....C..... 2030
MAJORITY CCACCGCCTCTCCCAGGAGCTTGCCATCCCCTACGAGGAGGCGGTGGCCTTCATTGAGCGCTACTTCCAG
DNAPTAQ ..........A.....T.....CCA..........T... 2094
DNAPTFL .....GG.....T..... 2091
DNAPTTH ...TA.G..........T..A.....A 2100

FIG. 2G

```
MAJORITY [SEQ ID NO:7]  AGCTTCCCCAAGGTGCGGGCCTGGATTGAGAAGACCCTGGAGGAGGGCAGGAGGCGGGGGTACGTGGAGA

DNAPTAQ  [SEQ ID NO:1]  ......................................................................  2164
DNAPTFL  [SEQ ID NO:2]  ....A.........................GG......C.........C.CC..........T.......  2161
DNAPTTR  [SEQ ID NO:3]  ..........................A..A.................G....A......C........A.  2170

MAJORITY                CCCTCTTCGGCCGCCGGCGCTACGTGCCCGACCTCAACGCCCGGGTGAAGAGCGTGCGGGAGGCGGCGGA

DNAPTAQ                 ................C...........A.....AG.G.............................C..  2234
DNAPTFL                 ......................T...................................C...........  2231
DNAPTTR                 ..........AA.AA........................................CA.......C.....  2240

MAJORITY                GCGCATGGCCTTCAACATGCCCGTCCAGGGCACCGCCGCCGACCTCATGAAGCTGGCCATGGTGAAGCTC

DNAPTAQ                 .........................................................T............  2304
DNAPTFL                 .....................G..........................................CG...T  2301
DNAPTTR                 ......................................................C...............  2310

MAJORITY                TTCCCCCGGCTXCAGGAAATGGGGGCCAGGATGCTCGTXCAGGTCCAGGACGAGCTGGTCCTCGAGGCCC

DNAPTAQ                 ......A....GG.........................T...............................  2374
DNAPTFL                 ...........T......C.......G........TT.G....G..........................  2371
DNAPTTR                 ........C..C.G...G.........C.C........C.................CC....G.......  2380

MAJORITY                CCAAAGAGCGGGCGGAGGXGGTGGCCGCTTTGGCCAAGGAGGTCATGGAGGGGGTCTATCCCCTGGCCGT

DNAPTAQ                 .A......A.........CC......CGGC.........................G..............  2444
DNAPTFL                 ....G..C.........AG...A..................................GG......CAG..  2441
DNAPTTR                 ..C...C......C....A......G................G.......AA..C.........C.....  2450
```

09940925 .022602

FIG. 2H

```
MAJORITY [SEQ ID NO:7] GCCCCTGGAGGTGGAGGTGGGGATGGGGGAGGACTGGCTCTCCGCCAAGGAGTAG

DNAPTAQ  [SEQ ID NO:1] .....A.....GA 2499
DNAPTFL  [SEQ ID NO:2] .....CC..... 2496
DNAPTTH  [SEQ ID NO:3] .....T.....GT... 2505
```

FIG. 3A

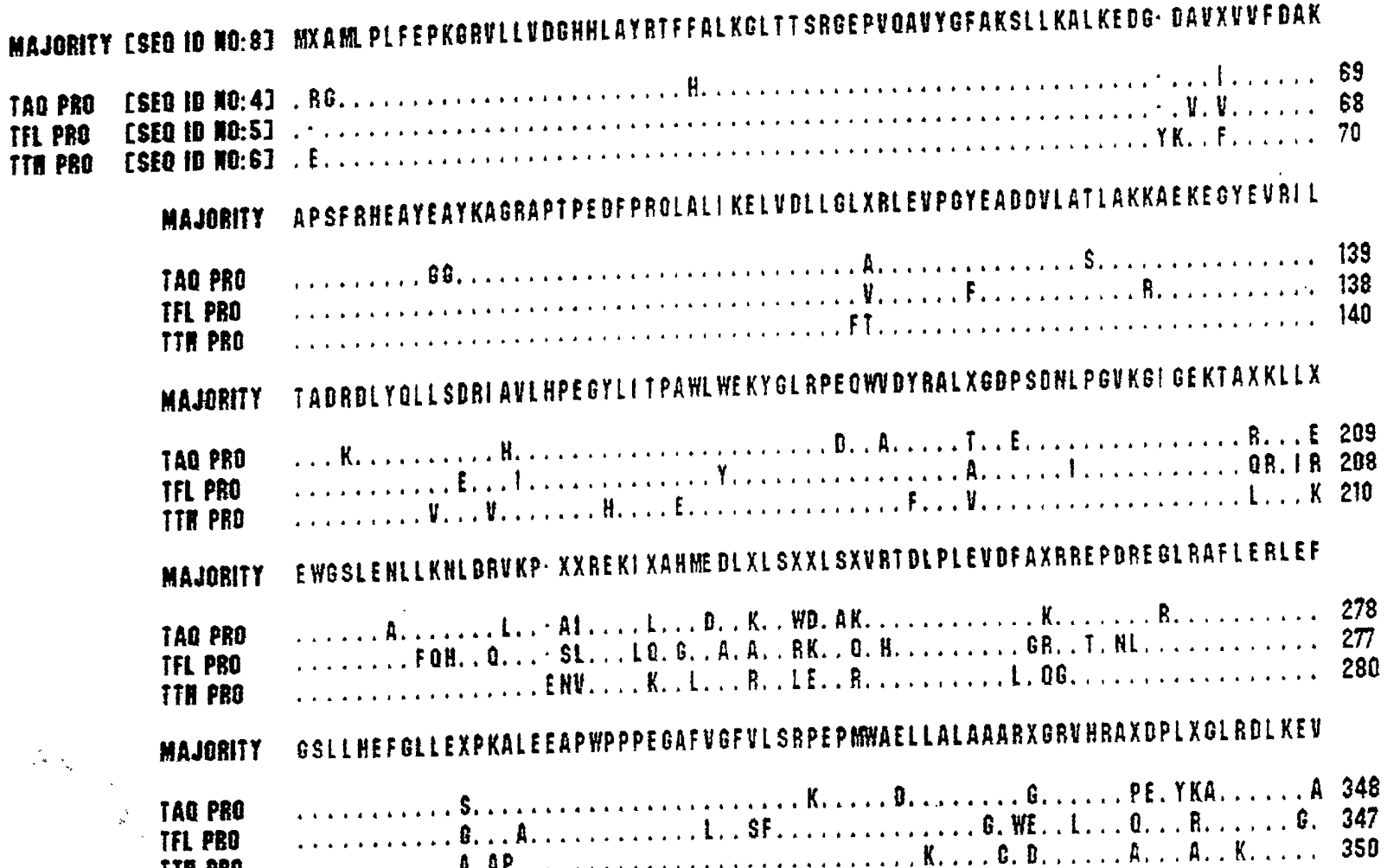

MAJORITY [SEQ ID NO:8] MXAML PLFEPKGRVLLVDGHHLAYRTFFALKGLTTSRGEPVQAVYGFAKSLLKALKEDG· DAVXVVFDAK
TAQ PRO [SEQ ID NO:4] 69
TFL PRO [SEQ ID NO:5] 68
TTH PRO [SEQ ID NO:6] 70
MAJORITY APSFRHEAYEAYKAGRAPTPEDFPRQLALIKELVDLLGLXRLEVPGYEADDVLATLAKKAEKEGYEVRIL
TAQ PRO 139
TFL PRO 138
TTH PRO 140
MAJORITY TADRDLYQLLSDRIAVLHPEGYLITPAWLWEKYGLRPEQWVDYRALXGDPSDNLPGVKGIGEKTAXKLLX
TAQ PRO 209
TFL PRO 208
TTH PRO 210
MAJORITY EWGSLENLLKNLDRVKP· XXREKIXAHMEDLXLSXXLSXVRTDLPLEVDFAXRREPDREGLRAFLERLEF
TAQ PRO 278
TFL PRO 277
TTH PRO 280
MAJORITY GSLLHEFGLLEXPKALEEAPWPPPEGAFVGFVLSRPEPMWAELLALAAARXGRVHRAXDPLXGLRDLKEV
TAQ PRO 348
TFL PRO 347
TTH PRO 350

FIG. 3B

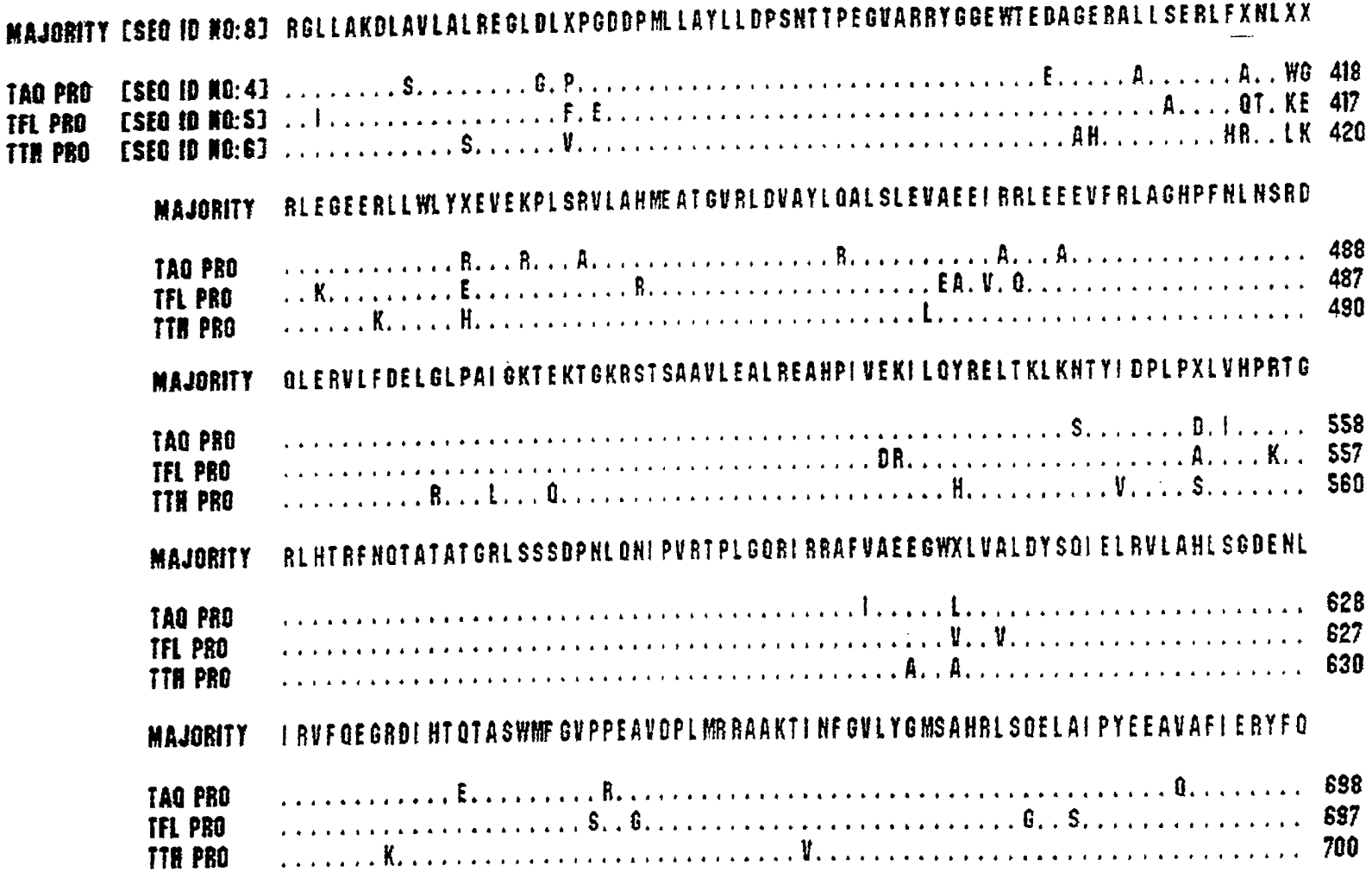

MAJORITY [SEQ ID NO:8] RGLLAKDLAVLALREGLDLXPGDDPMLLAYLLDPSNTTPEGVARRYGGEWTEDAGERALLSERLFXNLXX
TAQ PRO [SEQ ID NO:4] .....S.....G.P.....E.....A.....A..WG 418
TFL PRO [SEQ ID NO:5] ..I.....F.E.....A....QT.KE 417
TTH PRO [SEQ ID NO:6] .....S.....V.....AH.....HR..LK 420
MAJORITY RLEGEERLLWLYXEVEKPLSRVLAHMEATGVRLDVAYLQALSLEVAEEIRRLEEEVFRLAGHPFNLNSRD
TAQ PRO .....R...R...A.....R.....A...A..... 488
TFL PRO ..K.....E.....R.....EA.V.Q..... 487
TTH PRO .....K.....H.....L..... 490
MAJORITY QLERVLFDELGLPAIGKTEKTGKRSTSAAVLEALREAHPIVEKILQYRELTKLKNTYIDPLPXLVHPRTG
TAQ PRO .....S.....D.I..... 558
TFL PRO .....DR.....A....K.. 557
TTH PRO .....R...L...Q.....H.....V....S..... 560
MAJORITY RLHTRFNQTATATGRLSSSDPNLQNIPVRTPLGQRIRRAFVAEEGWXLVALDYSQIELRVLAHLSGDENL
TAQ PRO .....I.....L..... 628
TFL PRO .....V..V..... 627
TTH PRO .....A..A..... 630
MAJORITY IRVFQEGRDIHTQTASWMFGVPPEAVDPLMRRAAKTINFGVLYGMSAHRLSQELAIPYEEAVAFIERYFQ
TAQ PRO .....E.....R.....Q..... 698
TFL PRO .....S..G.....G..S..... 697
TTH PRO .....K.....V..... 700

FIG. 3C

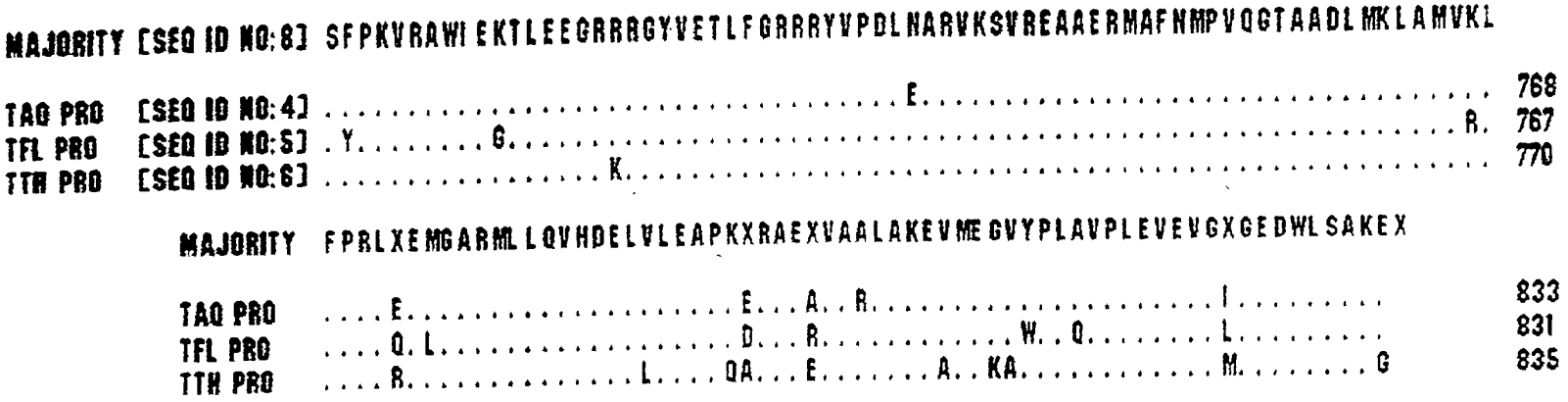
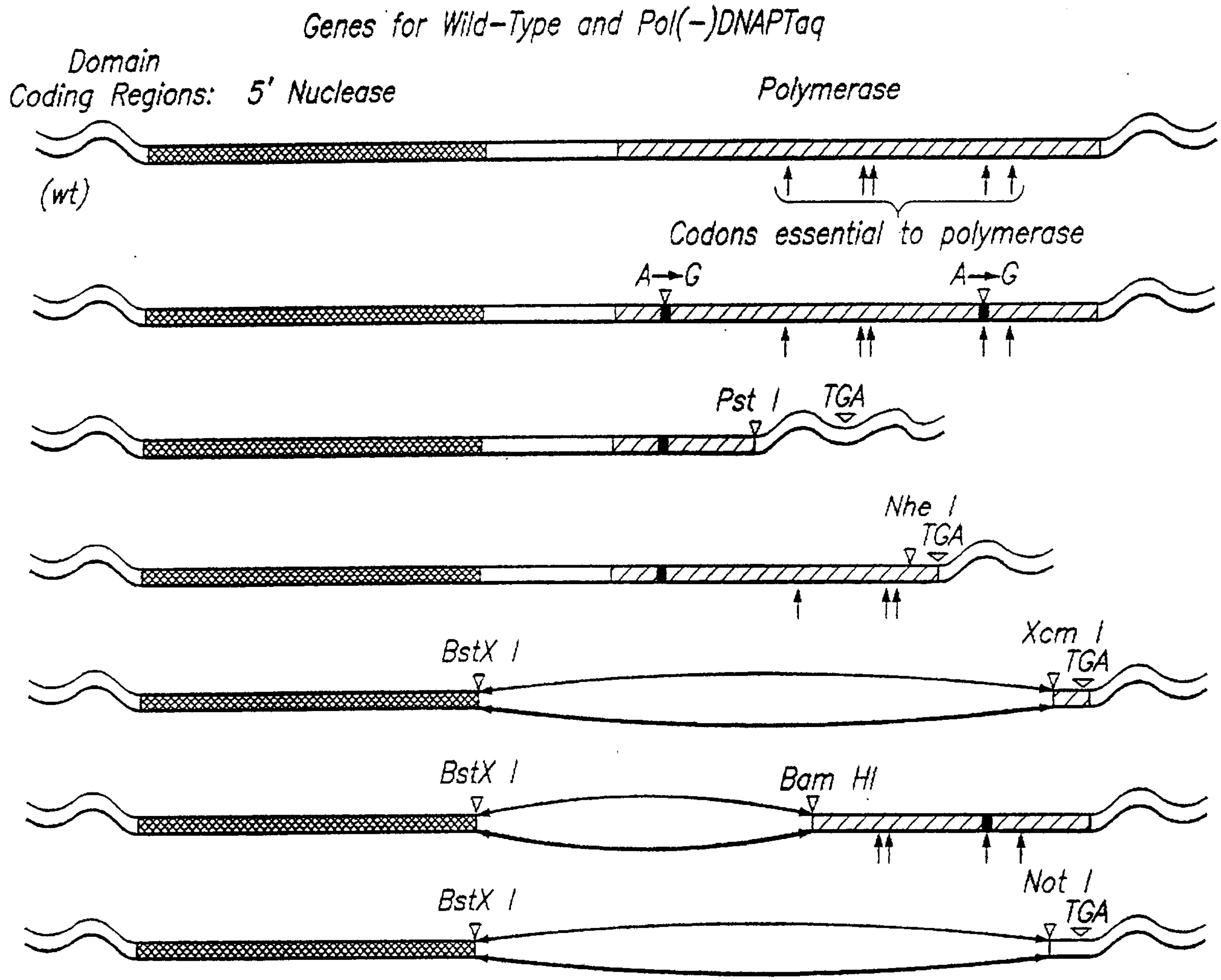

MAJORITY [SEQ ID NO:8] SFPKVRAWIEKTLEEGRRRGYVETLFGRRRYVPDLNARVKSVREAAERMAFNMPVQGTAADLMKLAMVKL
TAQ PRO [SEQ ID NO:4] .....E..... 768
TFL PRO [SEQ ID NO:5] .Y.....G.....R. 767
TTH PRO [SEQ ID NO:6] .....K..... 770
MAJORITY FPRLXEMGARMLLQVHDELVLEAPKXRAEXVAALAKEVMEGVYPLAVPLEVEVGXGEDWLSAKEX
TAQ PRO ....E.....E...A..R.....I..... 833
TFL PRO ....Q.L.....D...R.....W..Q.....L..... 831
TTH PRO ....R.....L....QA...E.....A..KA.....M.....G 835

FIG. 4A
FIG. 4B
FIG. 4C
FIG. 4D
FIG. 4E
FIG. 4F
FIG. 4G



Genes for Wild-Type and Pol(-) DNAPTfl

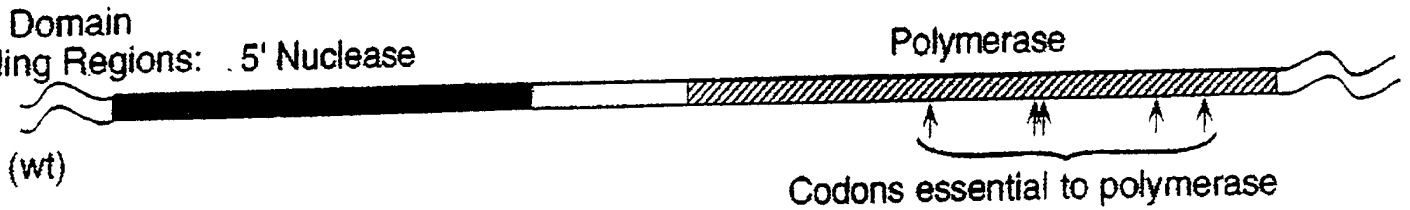


FIG. 5A

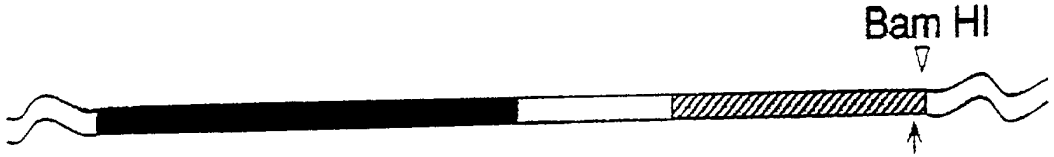


FIG. 5B

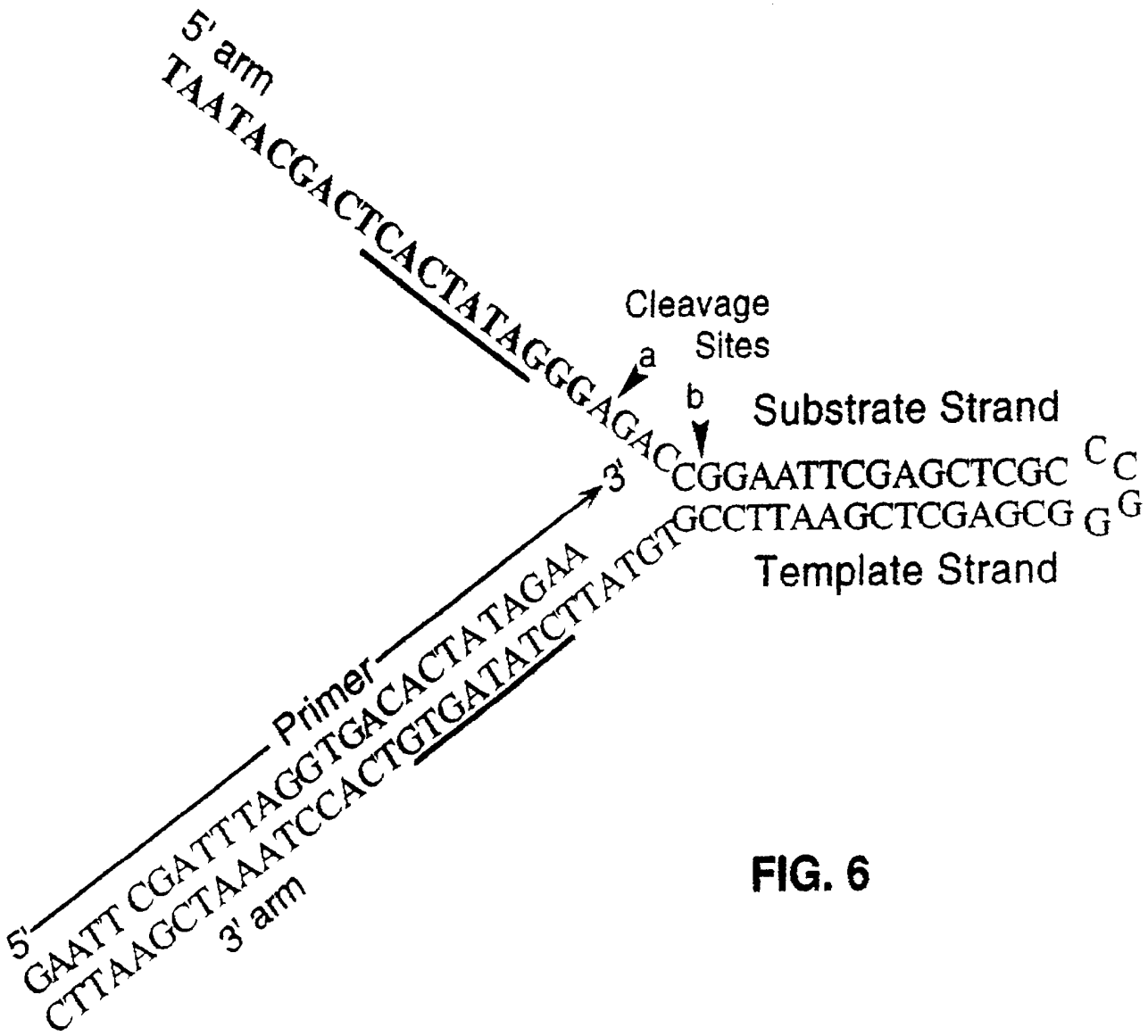


FIG. 6

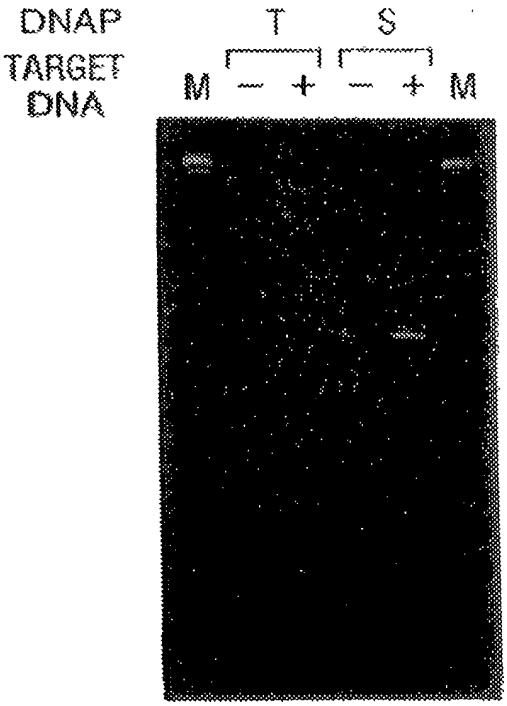


FIG. 7

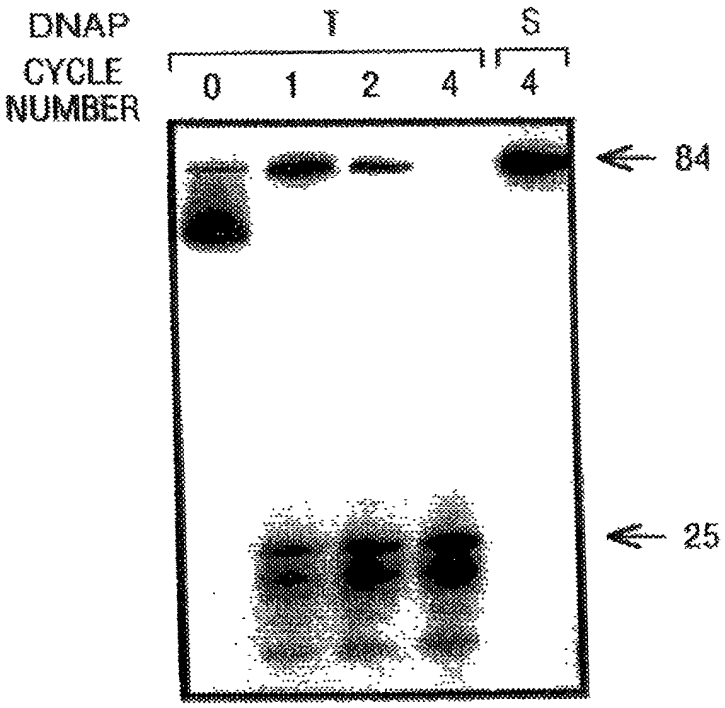


FIG. 8

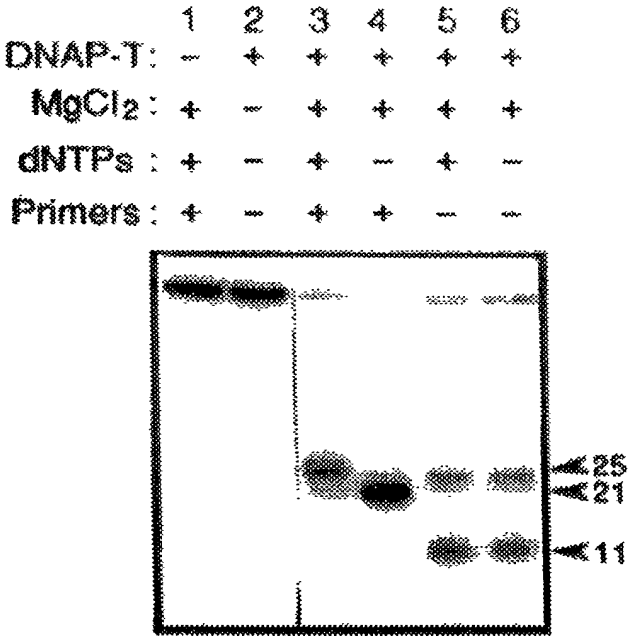


FIG. 9A

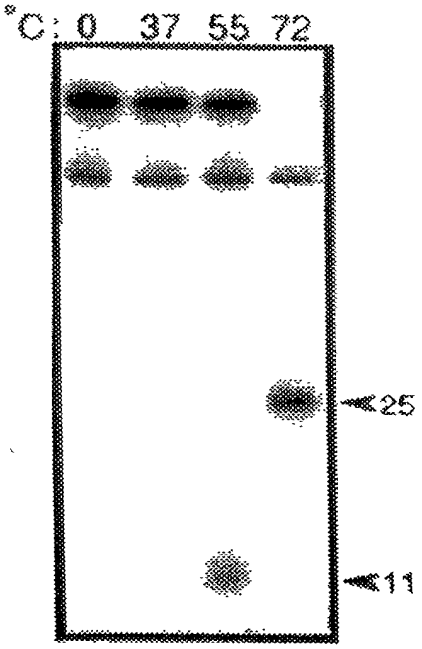


FIG. 9B

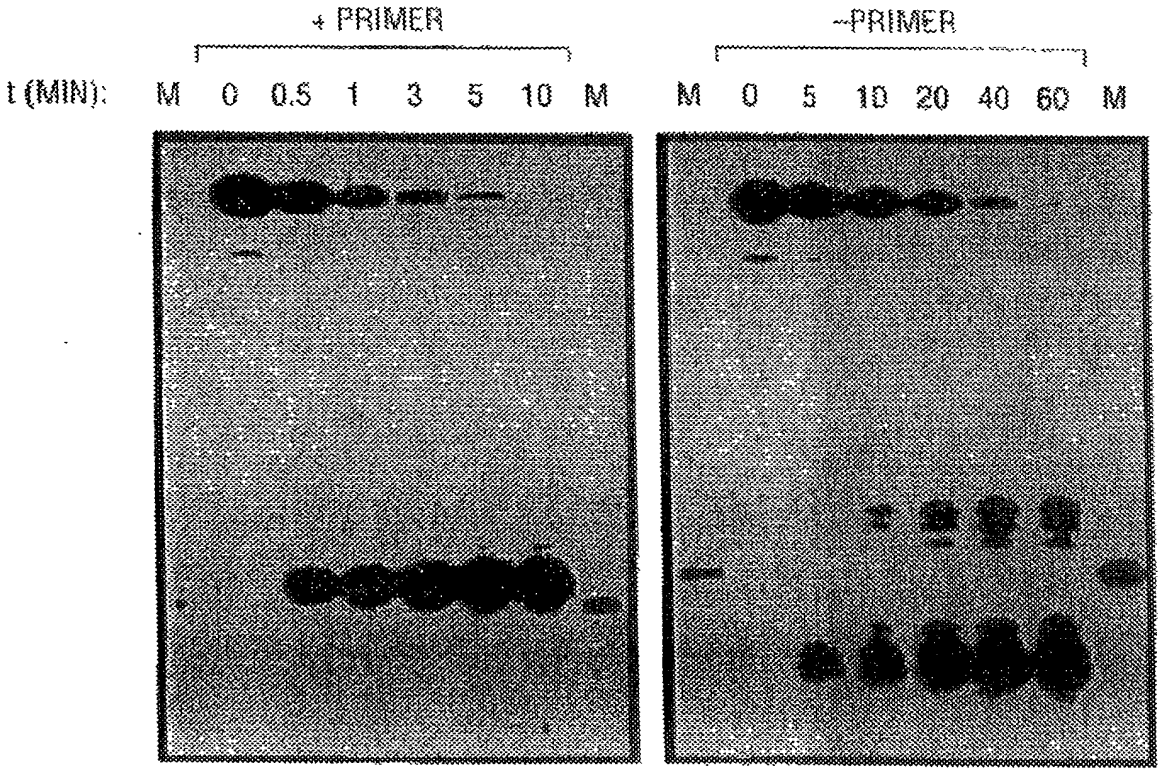


FIG. 10A

FIG. 10B

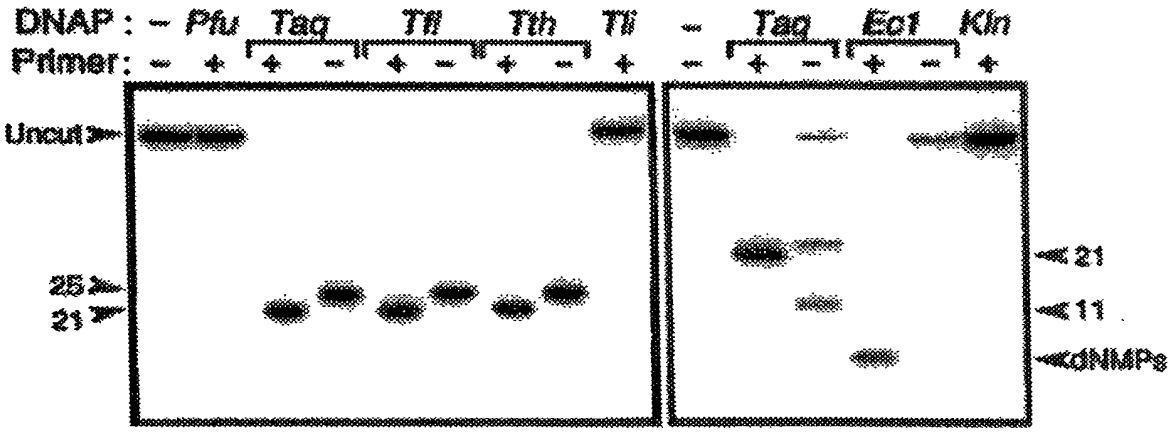
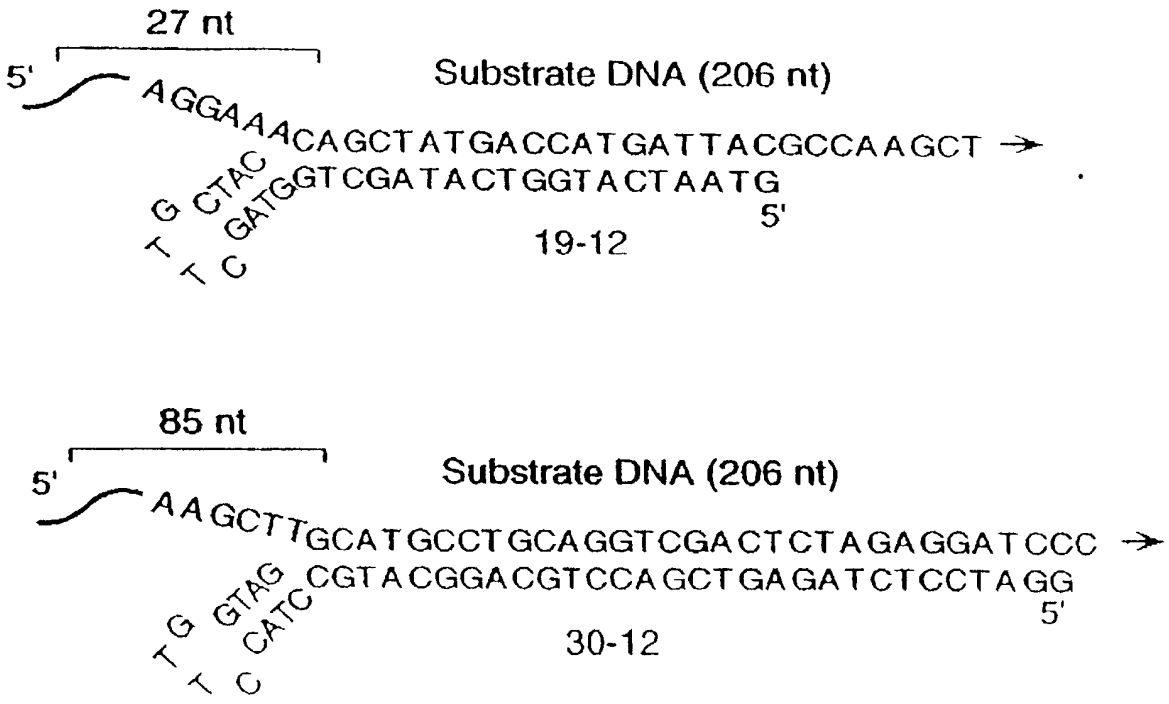


FIG. 11A

FIG. 11B

FIG. 12A


27 nt
5'
Substrate DNA (206 nt)
AGGAAACAGCTATGACCATGATTACGCCAAGCT
GTCGATACTGGTACTAATG
5'
19-12
85 nt
5'
Substrate DNA (206 nt)
AAGCTTGCATGCCTGCAGGTCGACTCTAGAGGATCCC
CGTACGGACGTCCAGCTGAGATCTCCTAGG
5'
30-12

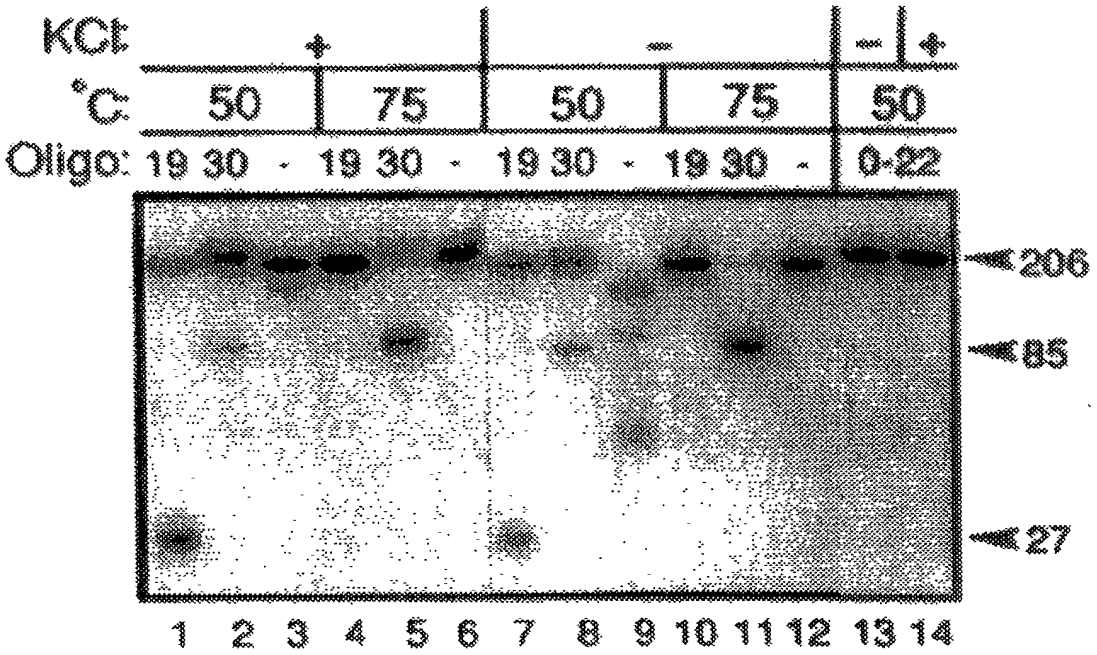


FIG. 12B

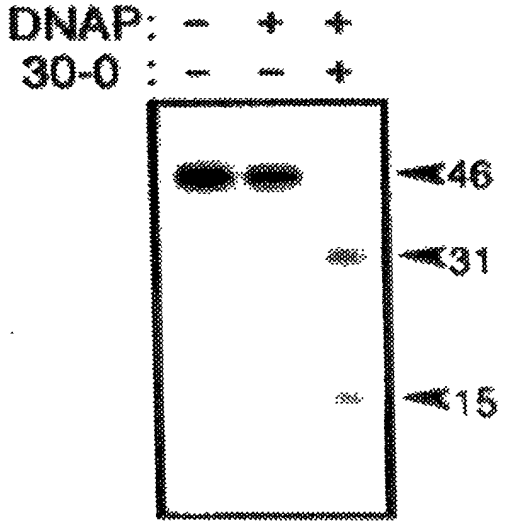


FIG. 13B

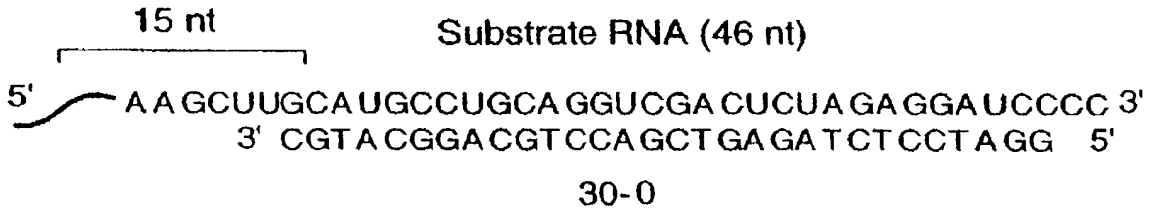

15 nt
Substrate RNA (46 nt)
5'
A A G C U U G C A U G C C U G C A G G U C G A C U C U A G A G G A U C C C C 3'
3' C G T A C G G A C G T C C A G C T G A G A T C T C C T A G G 5'
30-0

FIG. 13A

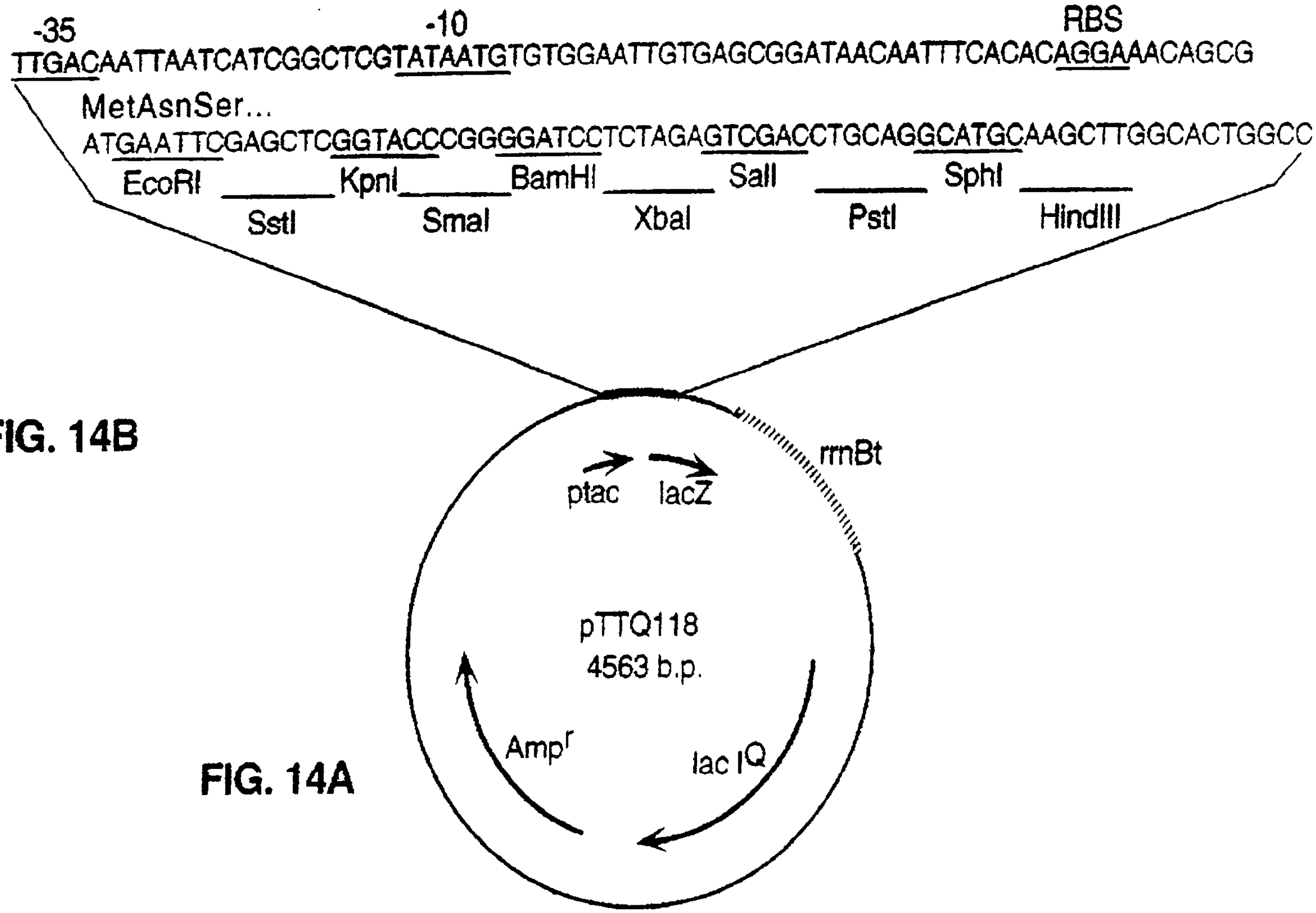


FIG. 14B

FIG. 14A

RBS: Ribosome binding site
ptac: Synthetic tac promoter
lac I^Q: Lac repressor gene
lacZ: Beta-galactosidase alpha fragment
rrnBt: E. coli rrnB transcription terminator

FIG. 14C

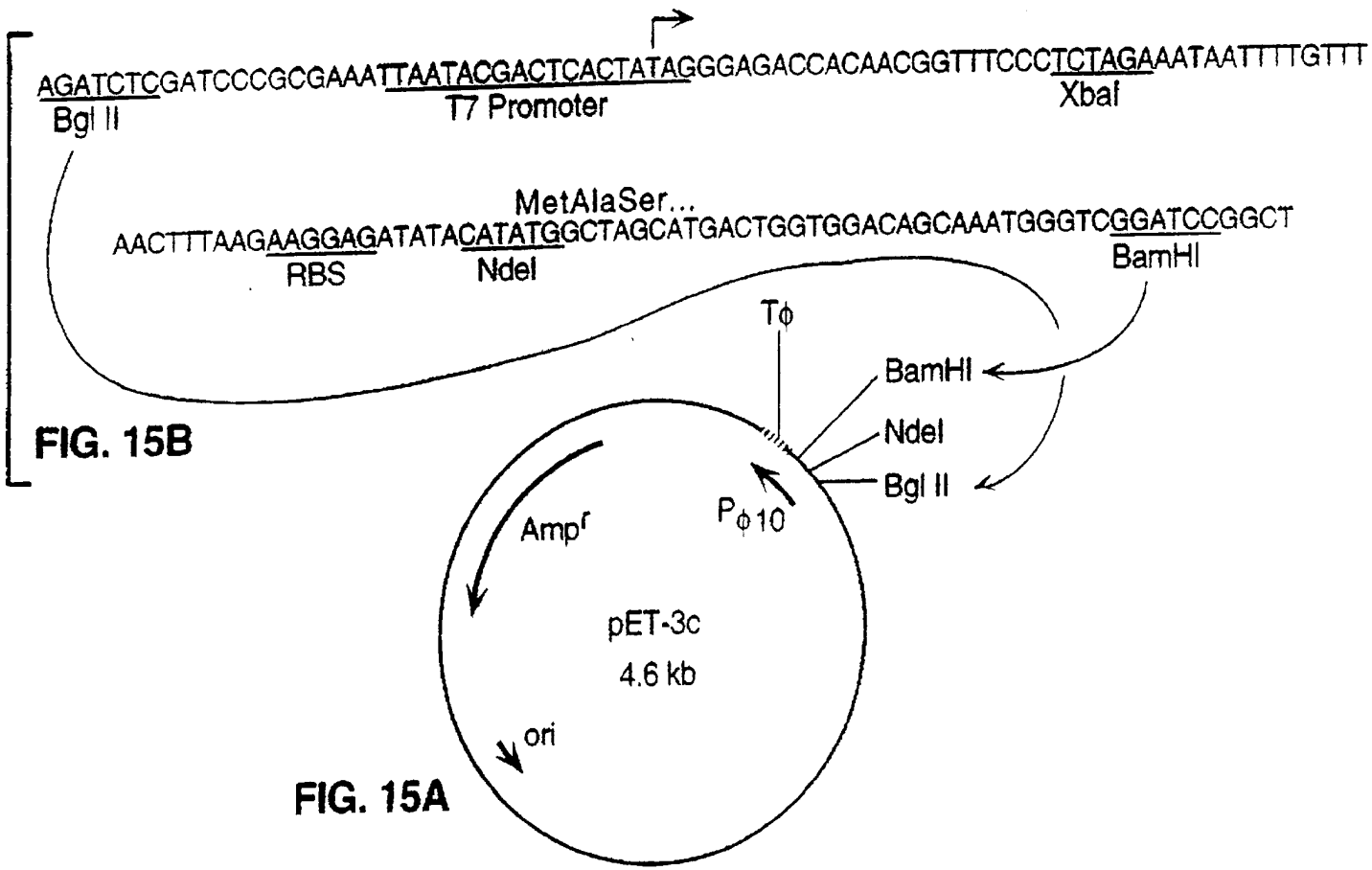


FIG. 15B

FIG. 15A

$P_{\phi 10}$: Bacteriophage T7 ϕ10 promoter RBS: Ribosome binding site

Tϕ: T7 ϕ Terminator

FIG. 15C

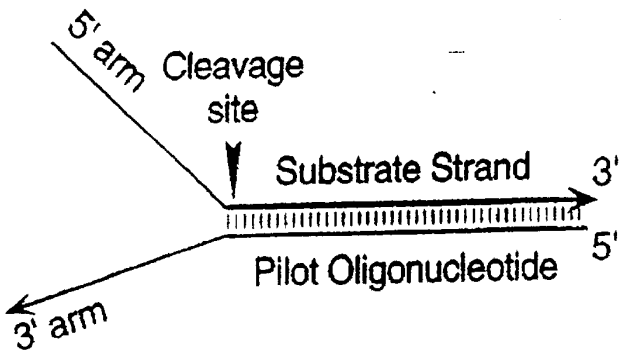


FIG. 16A

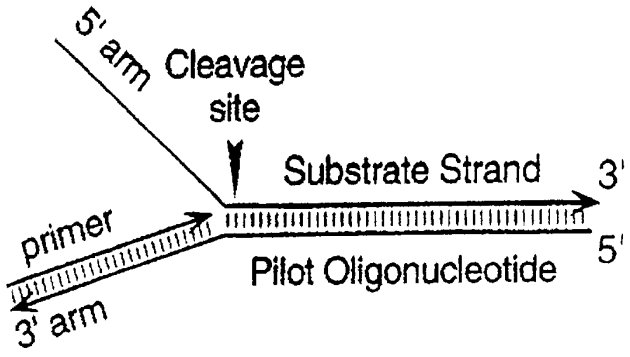


FIG. 16B

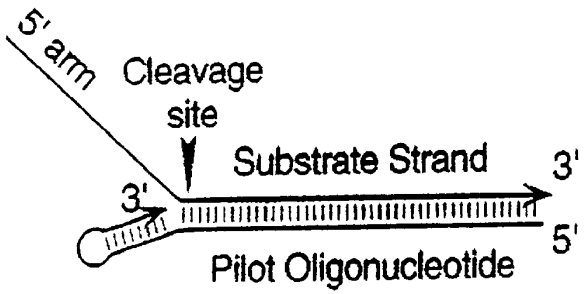


FIG. 16C

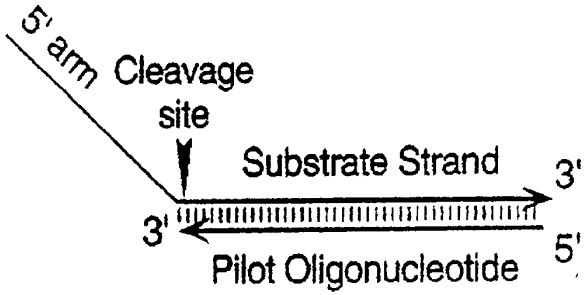


FIG. 16D

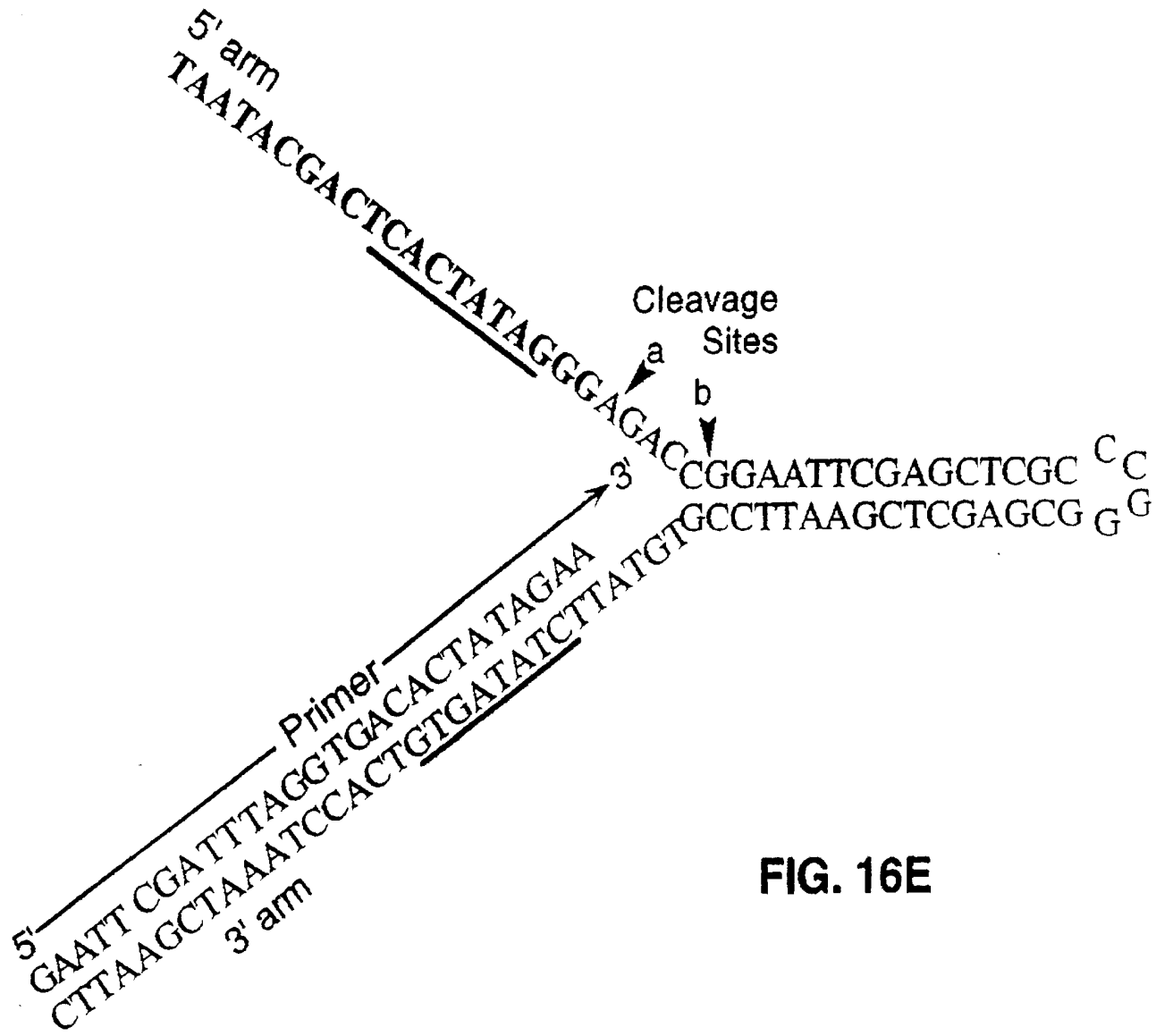

5' arm
TAATACGACTCACTATAGGGAGACC
Cleavage
Sites
a
b
3'
CGGAATTCGAGCTCGC C C
GCCTTAAGCTCGAGCG G G
Primer
5'
GAATT CGATTTAGGTGACACTATAGAA
CTTAAGCTAAATCCACTGTGATATCTTATGT
3' arm

FIG. 16E

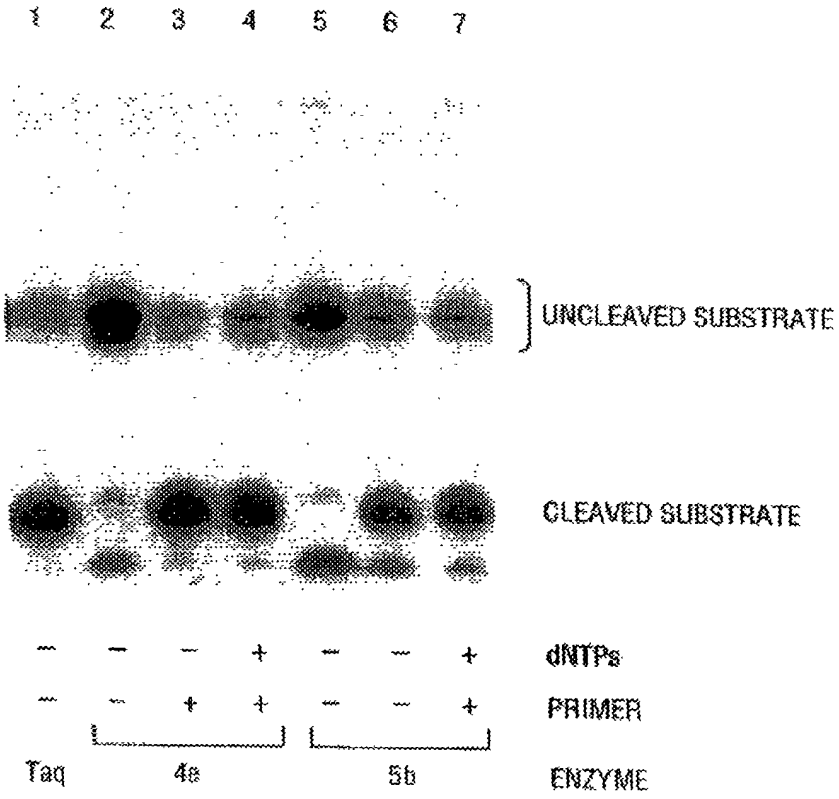

1 2 3 4 5 6 7
UNCLEAVED SUBSTRATE
CLEAVED SUBSTRATE
– – – + – – + dNTPs
– – + + – – + PRIMER
Taq 4a 5b ENZYME

FIG. 17

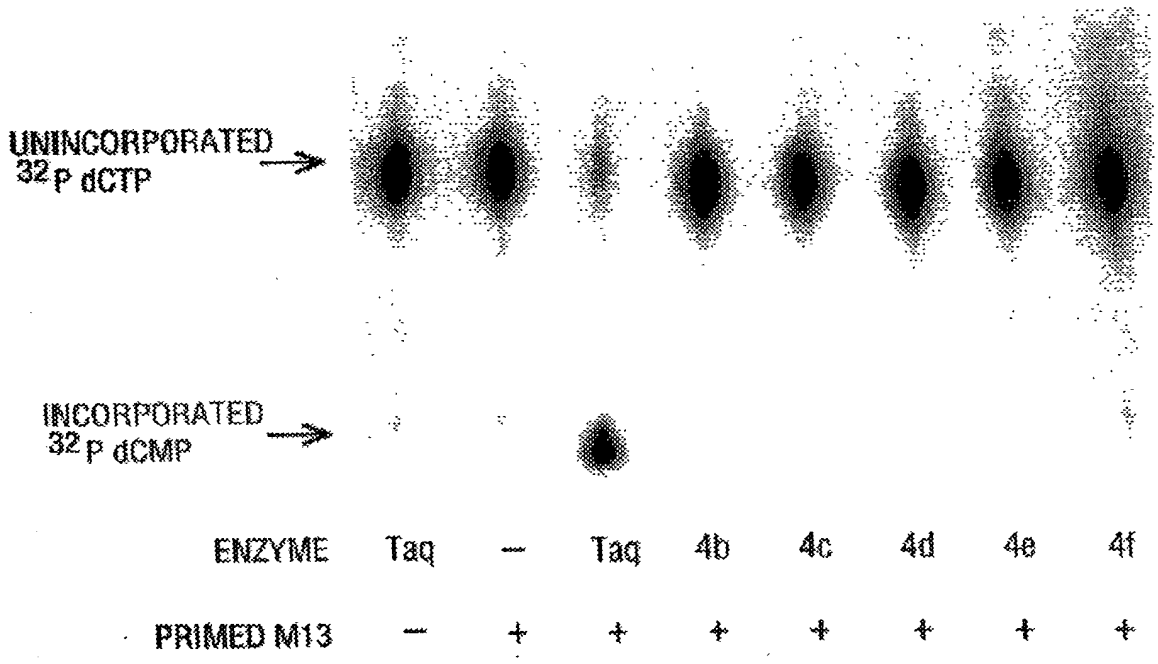

UNINCORPORATED
32P dCTP
INCORPORATED
32P dCMP
ENZYME Taq — Taq 4b 4c 4d 4e 4f
PRIMED M13 — + + + + + + +

FIG. 18

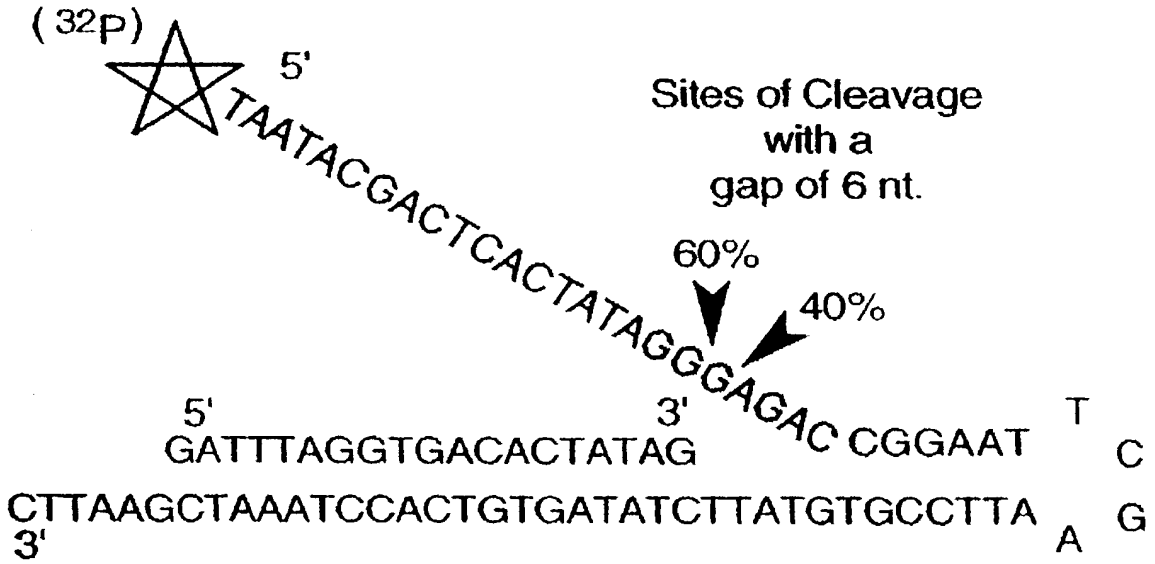

(32P)
5'
TAATACGACTCACTATAGGGAGAC
Sites of Cleavage
with a
gap of 6 nt.
60%
40%
5'
3'
GATTTAGGTGACACTATAG
CGGAAT
T
C
CTTAAGCTAAATCCACTGTGATATCTTATGTGCCTTA
A
G
3'

FIG. 19A

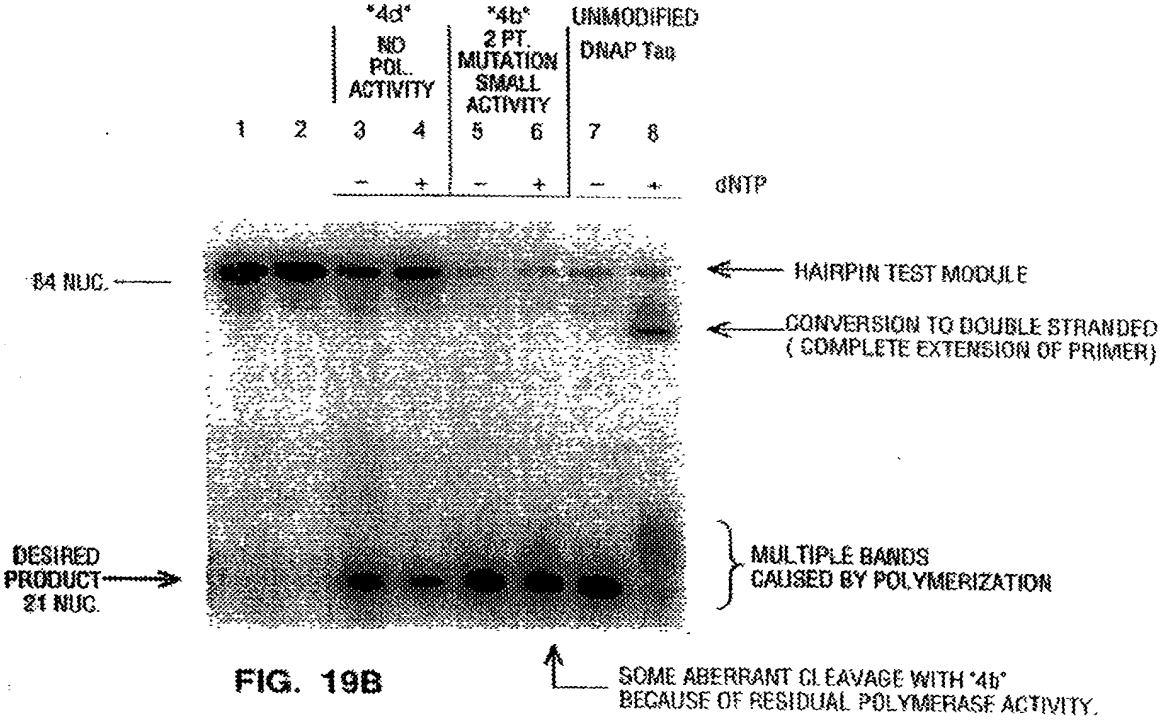

"4d"
NO POL. ACTIVITY
"4b"
2 PT. MUTATION SMALL ACTIVITY
UNMODIFIED DNAP Taq
1 2 3 4 5 6 7 8
– + – + – + dNTP
84 NUC.
HAIRPIN TEST MODULE
CONVERSION TO DOUBLE STRANDED (COMPLETE EXTENSION OF PRIMER)
DESIRED PRODUCT 21 NUC.
MULTIPLE BANDS CAUSED BY POLYMERIZATION
SOME ABERRANT CLEAVAGE WITH "4b" BECAUSE OF RESIDUAL POLYMERASE ACTIVITY.

FIG. 19B

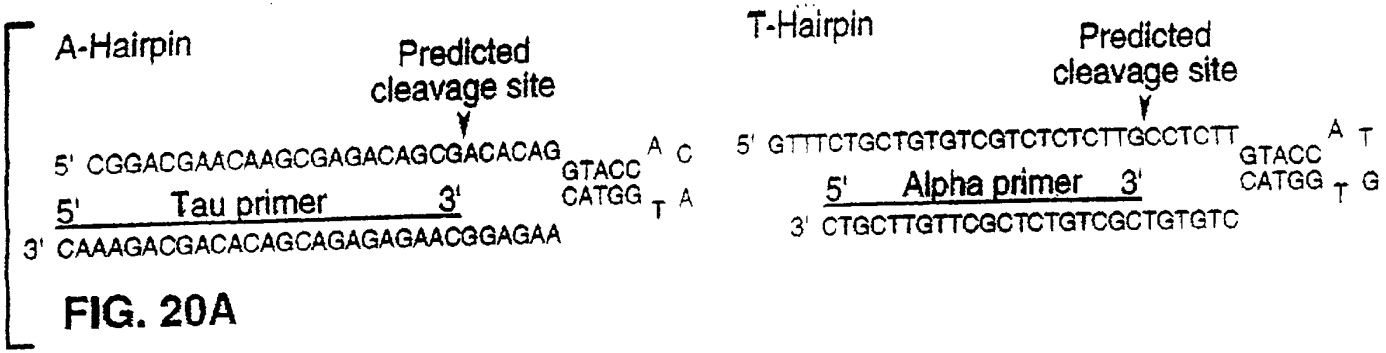


FIG. 20A

Sequence of alpha primer:

5' GACGAACAAGCGAGACAGCG 3'

FIG. 20B

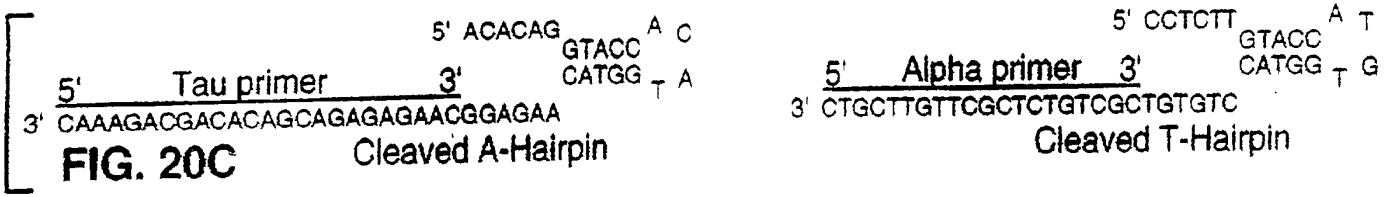


FIG. 20C

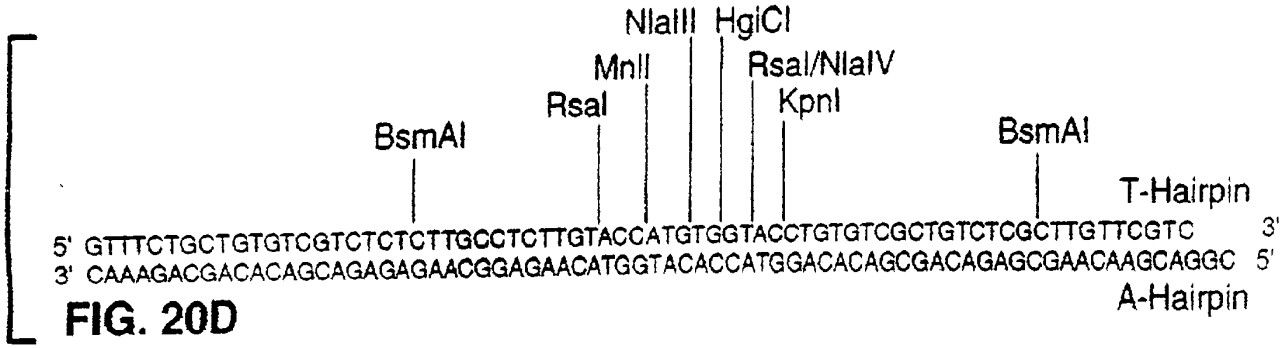


FIG. 20D

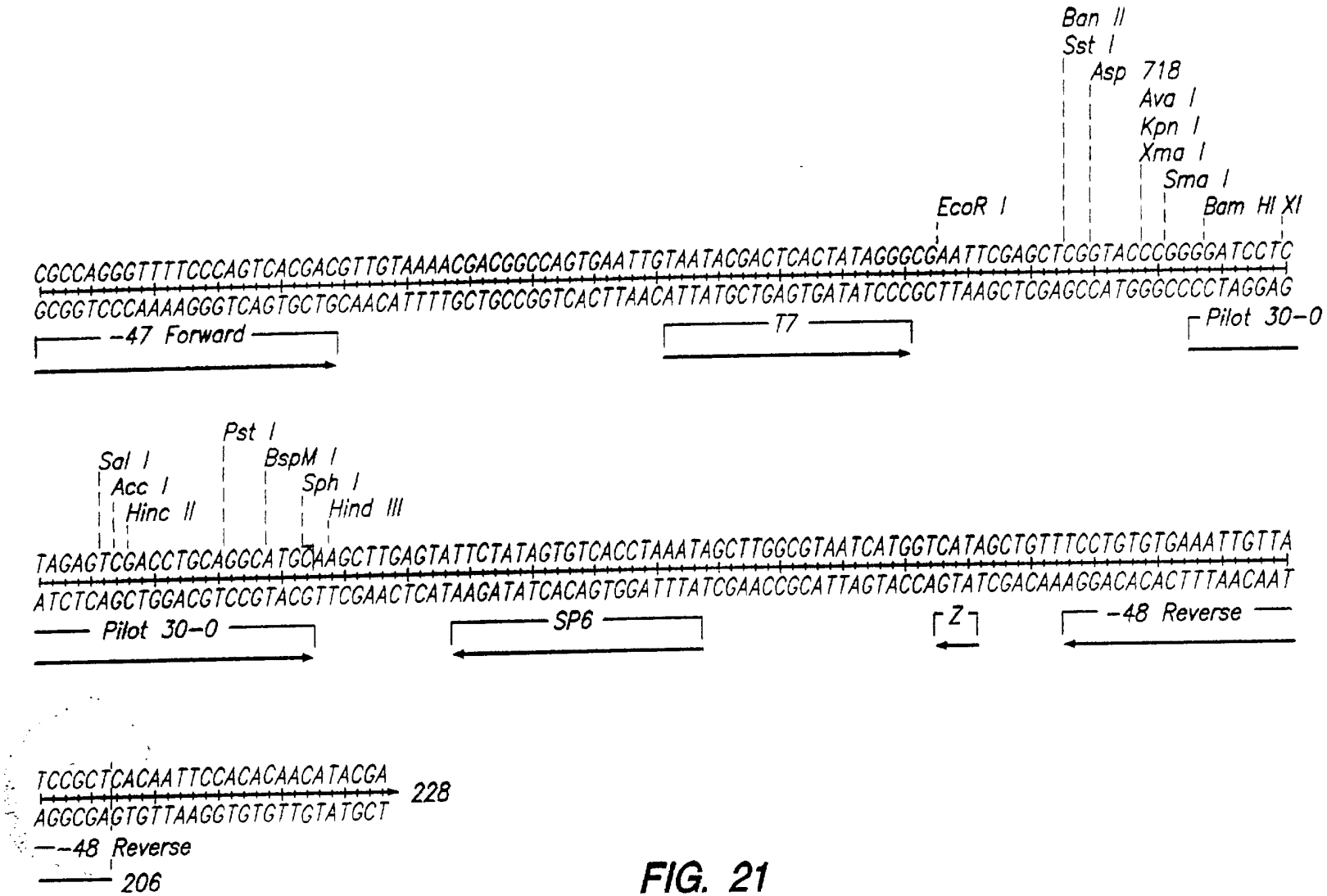

Ban II
Sst I
Asp 718
Ava I
Kpn I
Xma I
Sma I
EcoR I
Bam HI XI
CGCCAGGGTTTTCCCAGTCACGACGTTGTAAAACGACGGCCAGTGAATTGTAATACGACTCACTATAGGGCGAATTCGAGCTCGGTACCCGGGGATCCTC
GCGGTCCCAAAAGGGTCAGTGCTGCAACATTTTGCTGCCGGTCACTTAACATTATGCTGAGTGATATCCCGCTTAAGCTCGAGCCATGGGCCCCTAGGAG
-47 Forward
T7
Pilot 30-0
Pst I
Sal I
BspM I
Acc I
Sph I
Hinc II
Hind III
TAGAGTCGACCTGCAGGCATGCAAGCTTGAGTATTCTATAGTGTCACCTAAATAGCTTGGCGTAATCATGGTCATAGCTGTTTCCTGTGTGAAATTGTTA
ATCTCAGCTGGACGTCCGTACGTTCGAACTCATAAGATATCACAGTGGATTTATCGAACCGCATTAGTACCAGTATCGACAAAGGACACACTTTAACAAT
Pilot 30-0
SP6
Z
-48 Reverse
TCCGCTCACAATTCCACACAACATACGA
228
AGGCGAGTGTTAAGGTGTGTTGTATGCT
--48 Reverse
206

FIG. 21

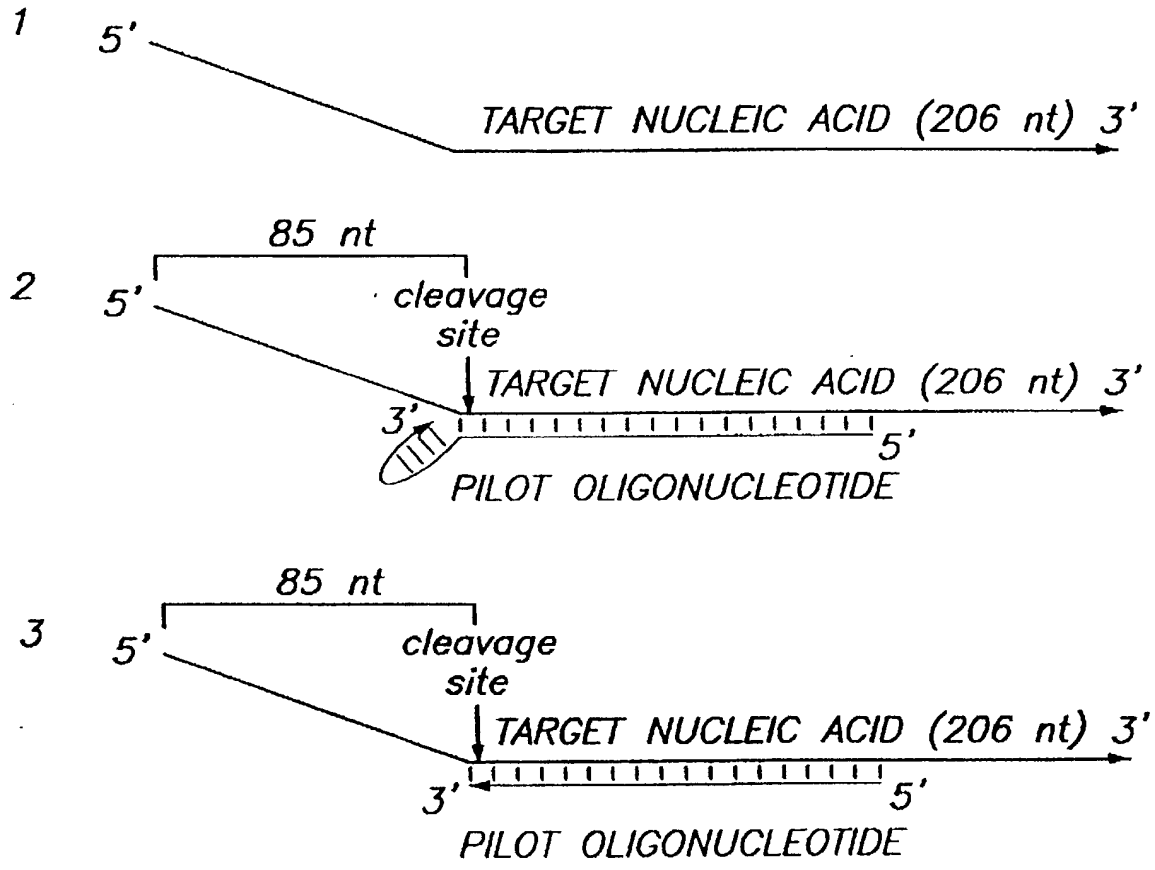


FIG. 22A

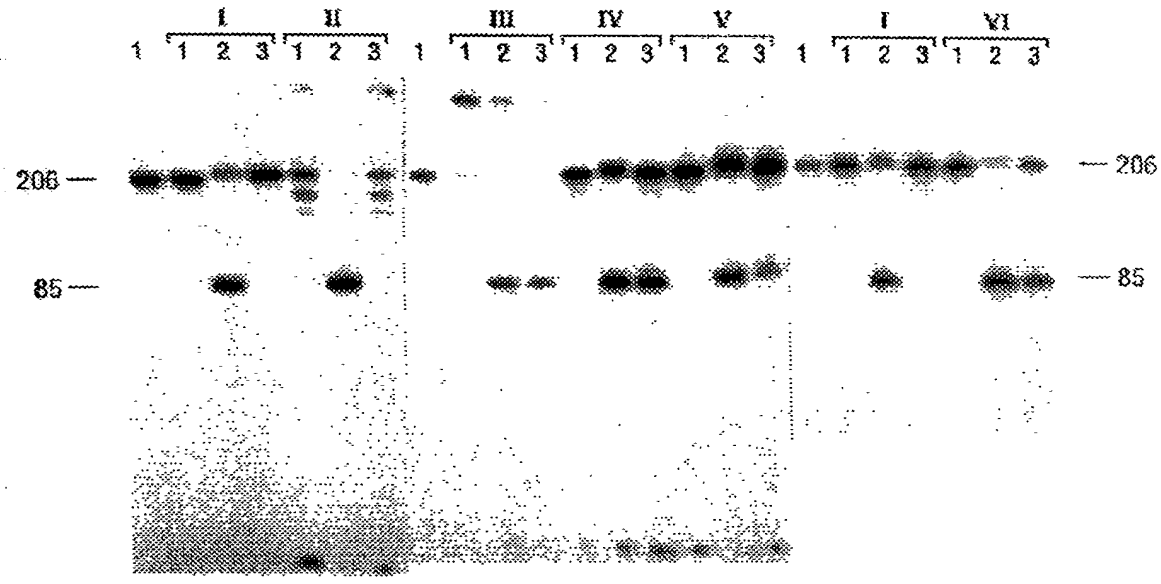


FIG. 22B

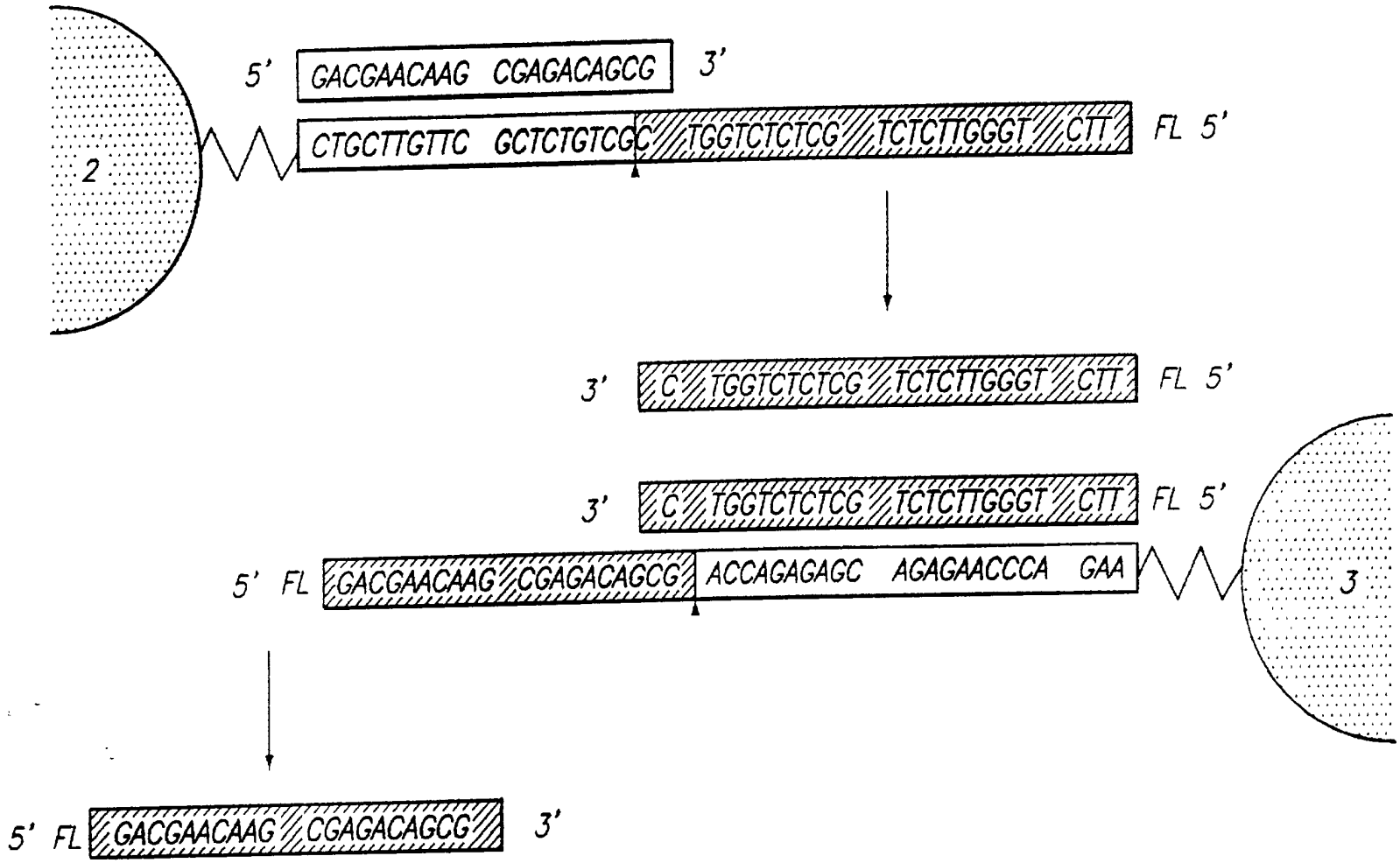

5' GACGAACAAG CGAGACAGCG 3'
CTGCTTGTTC GCTCTGTCGC TGGTCTCTCG TCTCTTGGGT CTT FL 5'
2
3' C TGGTCTCTCG TCTCTTGGGT CTT FL 5'
3' C TGGTCTCTCG TCTCTTGGGT CTT FL 5'
5' FL GACGAACAAG CGAGACAGCG ACCAGAGAGC AGAGAACCCA GAA
3
5' FL GACGAACAAG CGAGACAGCG 3'

FIG. 23

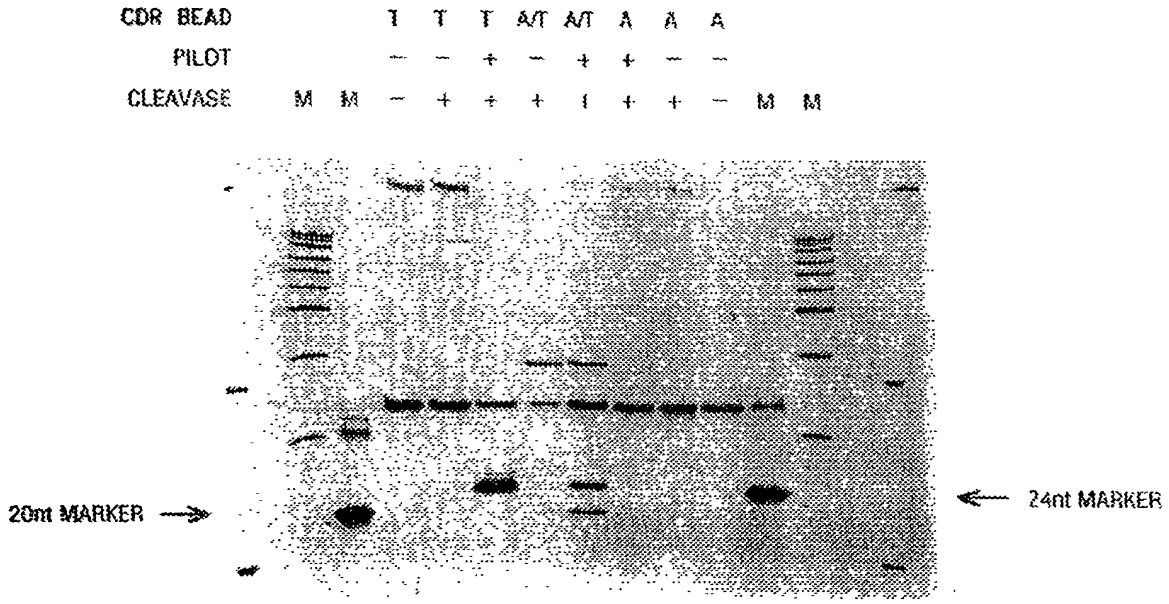

CDR BEAD
PILOT
CLEAVASE
T T T A/T A/T A A A
M M – + + + + + + – M M
20nt MARKER
24nt MARKER

FIG. 24

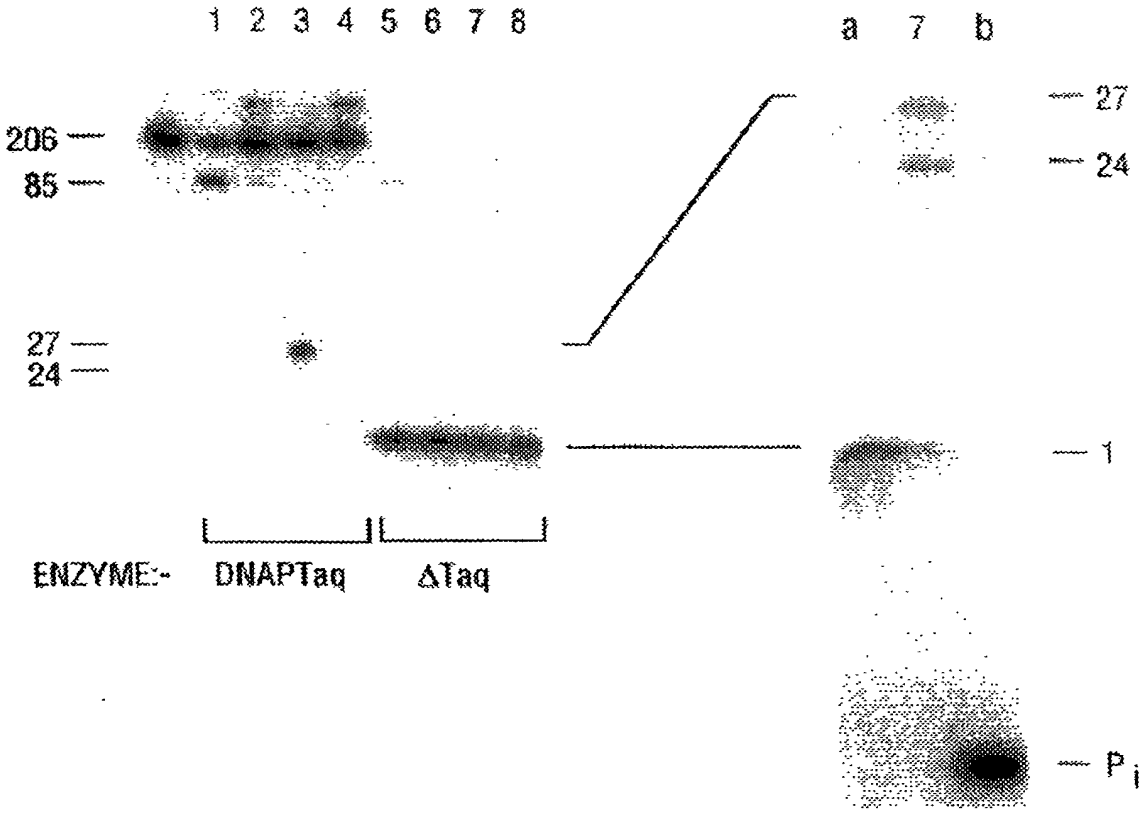


FIG. 25A

FIG. 25B

FIG. 26A

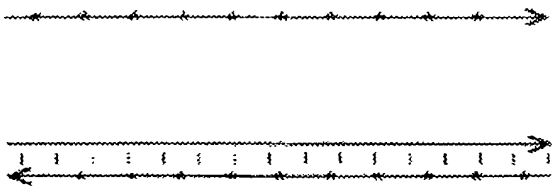
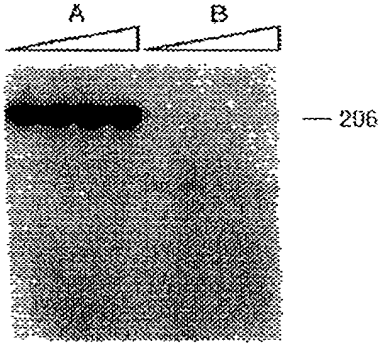


FIG. 26B

* = ^{32}P



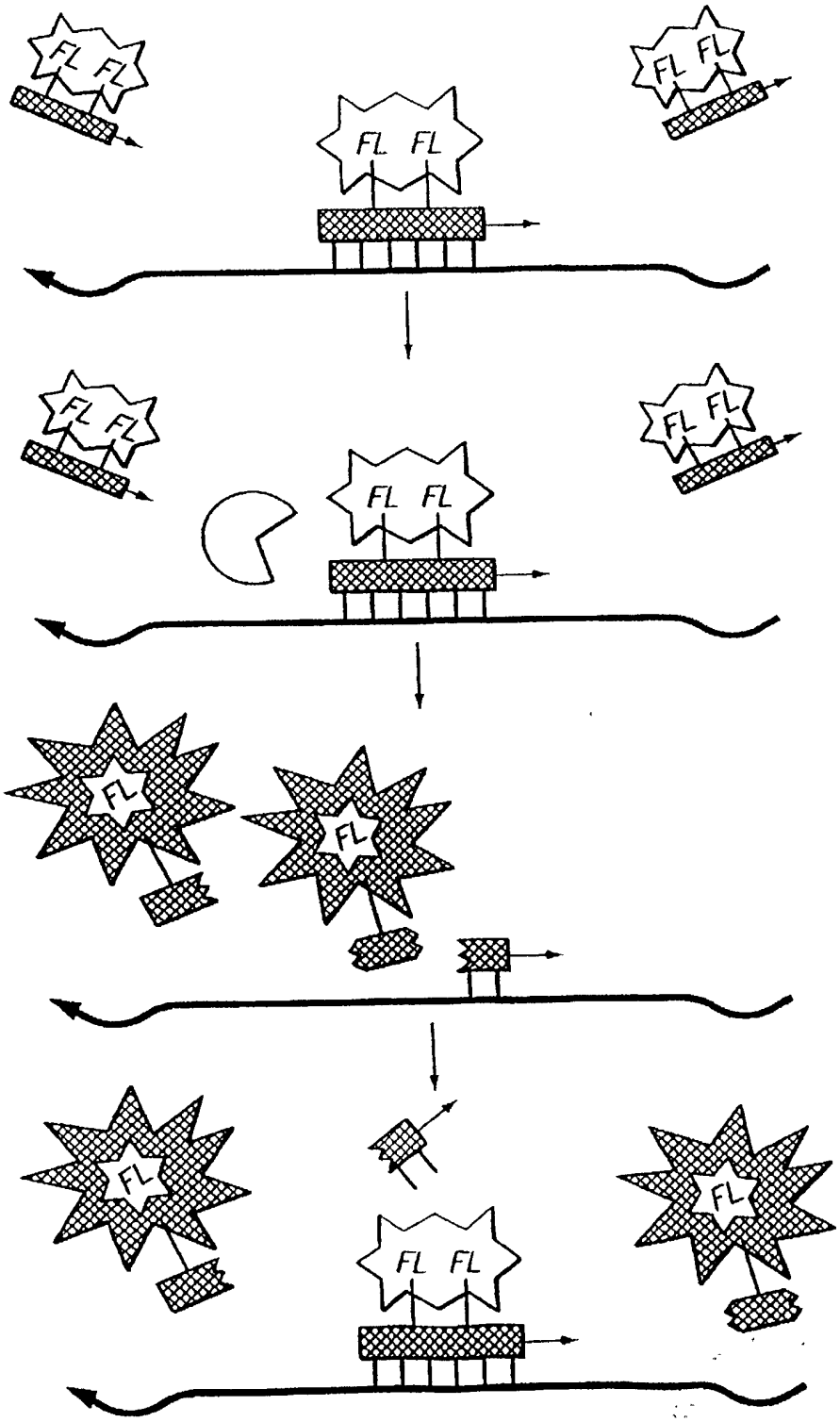


FIG. 27

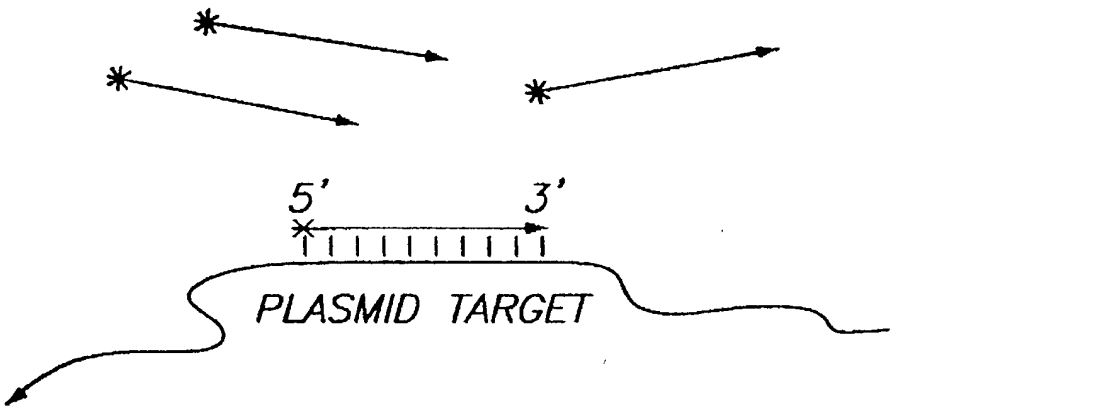


FIG. 28A

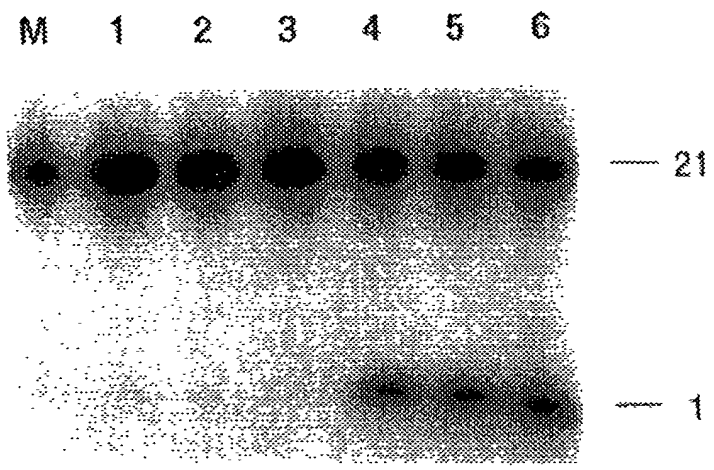


FIG. 28B

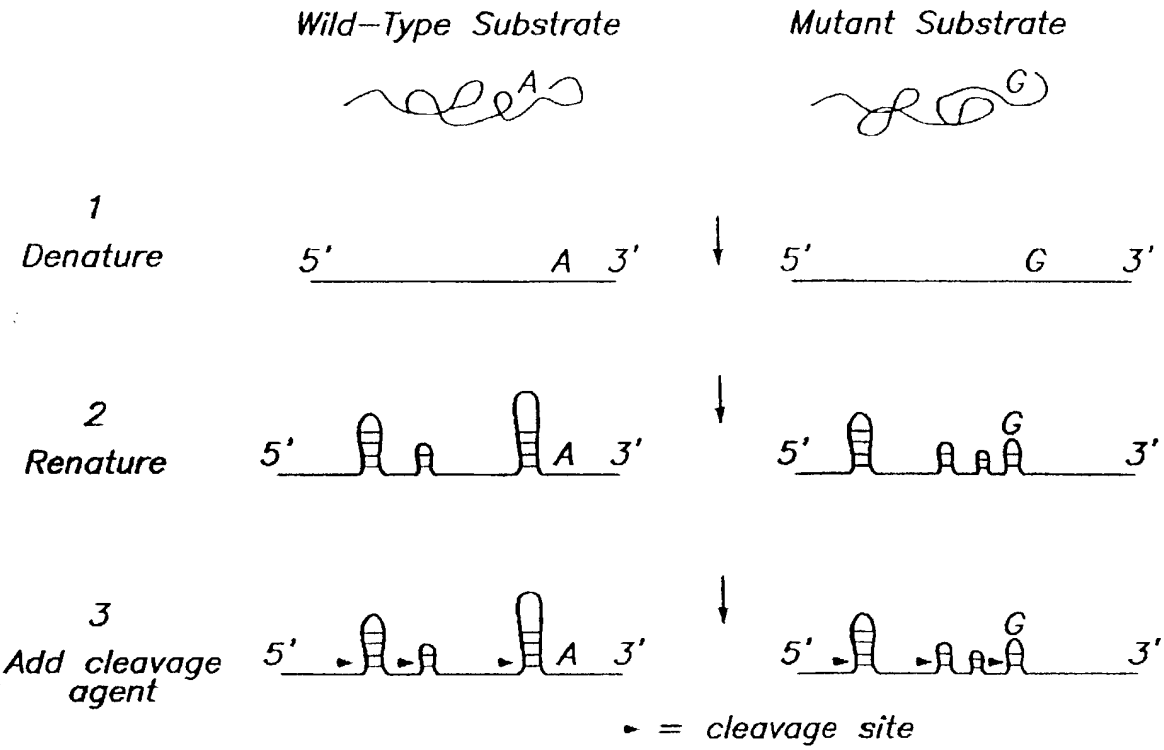

Wild-Type Substrate
Mutant Substrate
A
G
1
Denature
5' A 3'
5' G 3'
2
Renature
5' A 3'
5' G 3'
3
Add cleavage agent
5' A 3'
5' G 3'
► = cleavage site
4
Resolve reaction products
uncut control
wild-type
mutant
5
Detect unique cleavage "fingerprint"

FIG. 29

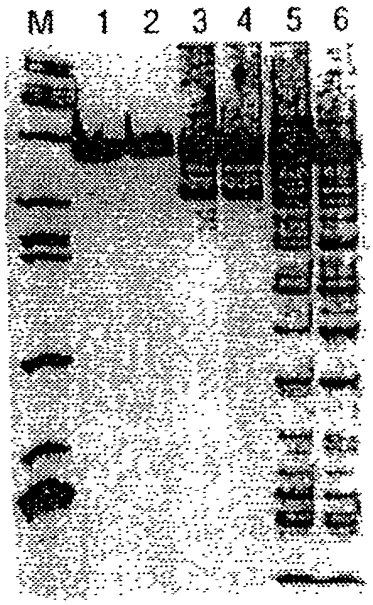


FIG. 30

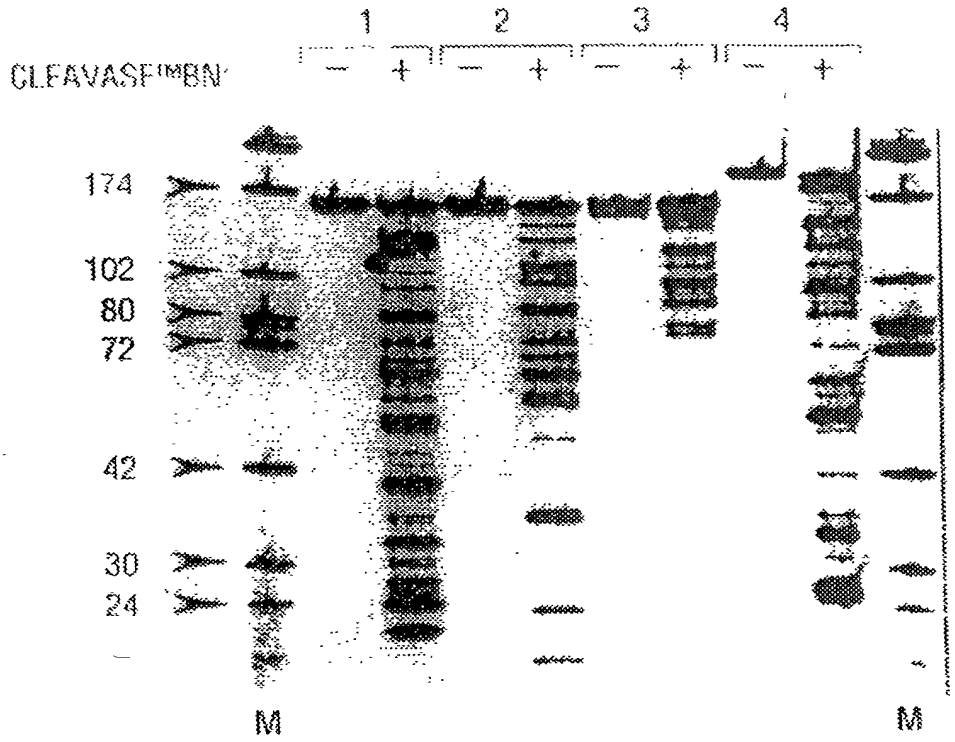


FIG. 31

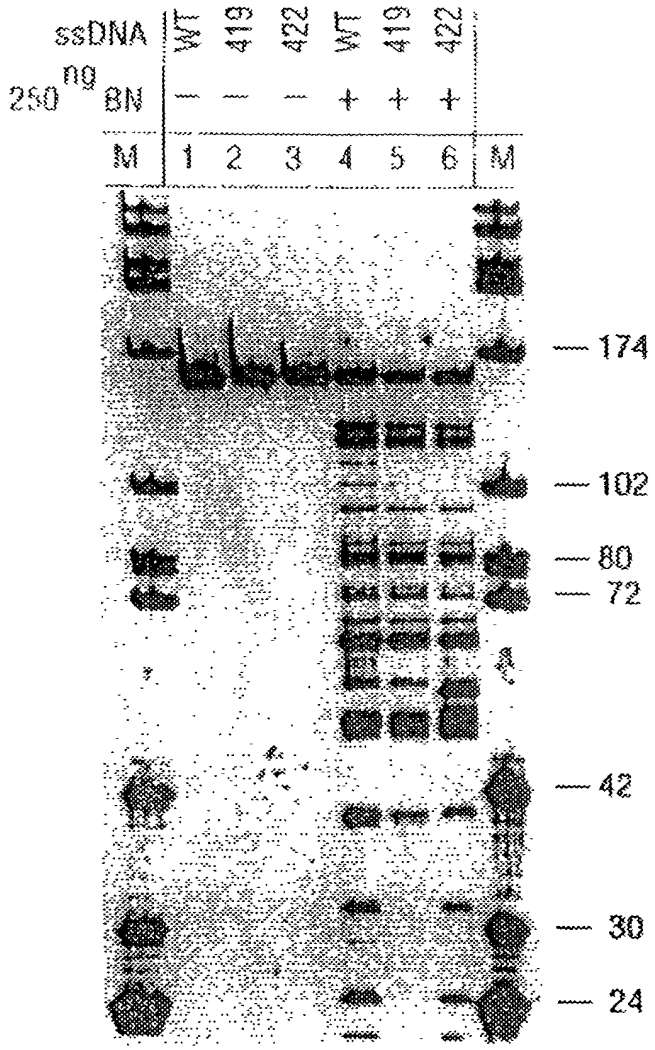

ssDNA
WT
419
422
WT
419
422
250 ng BN
—
—
—
+
+
+
M
1
2
3
4
5
6
M
174
102
80
72
42
30
24

FIG. 32

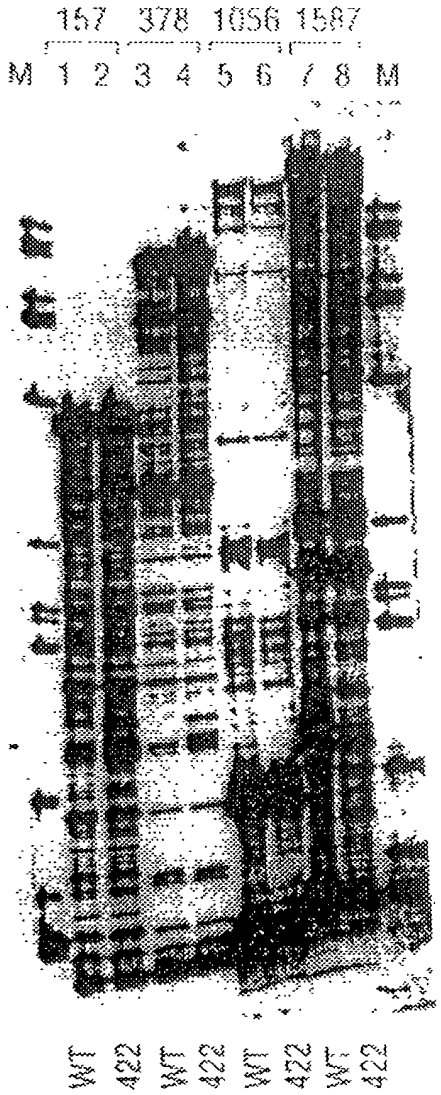


FIG. 33

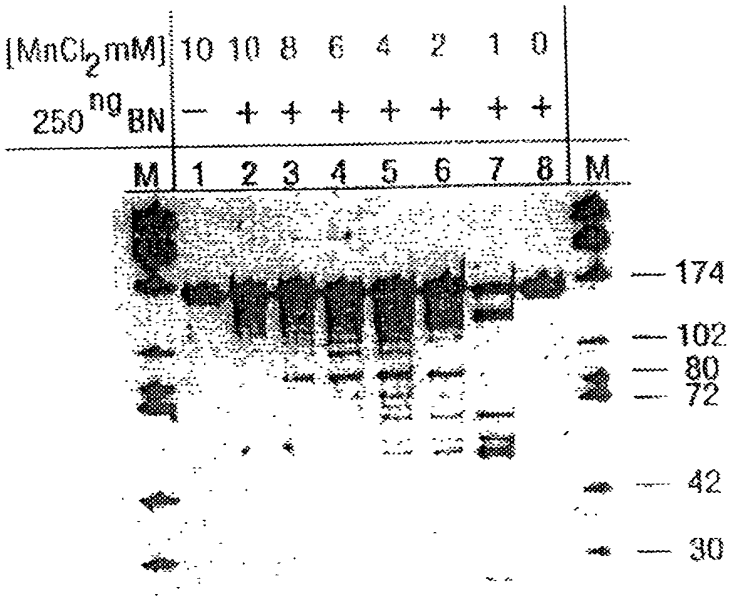


FIG. 34

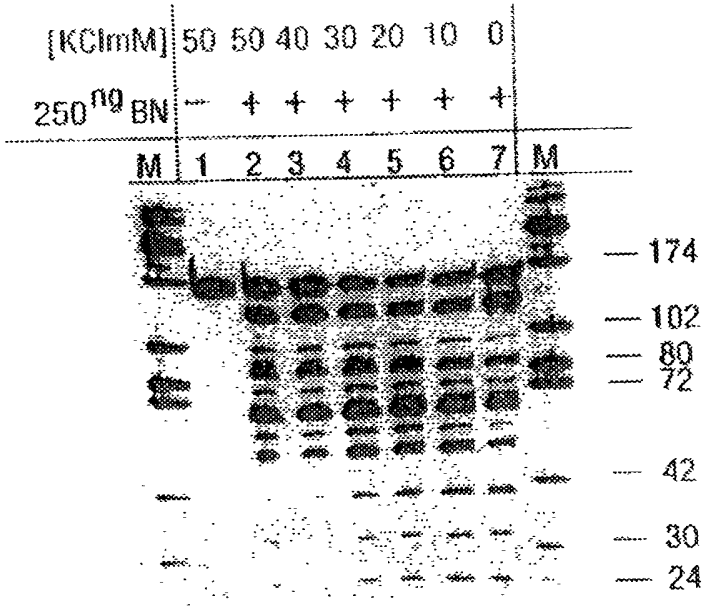

[KClmM] 50 50 40 30 20 10 0
250ng BN – + + + + + +
M 1 2 3 4 5 6 7 M
174
102
80
72
42
30
24

FIG. 35

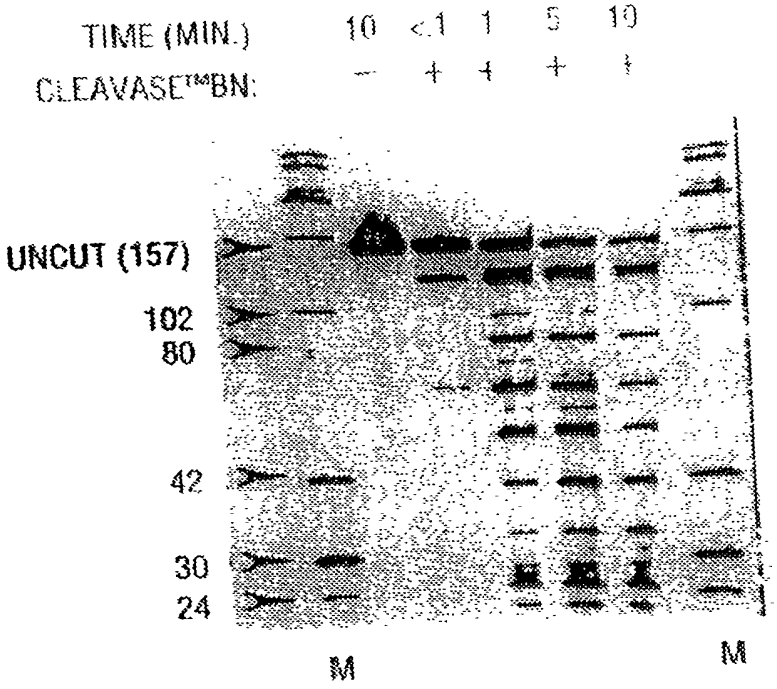


FIG. 36

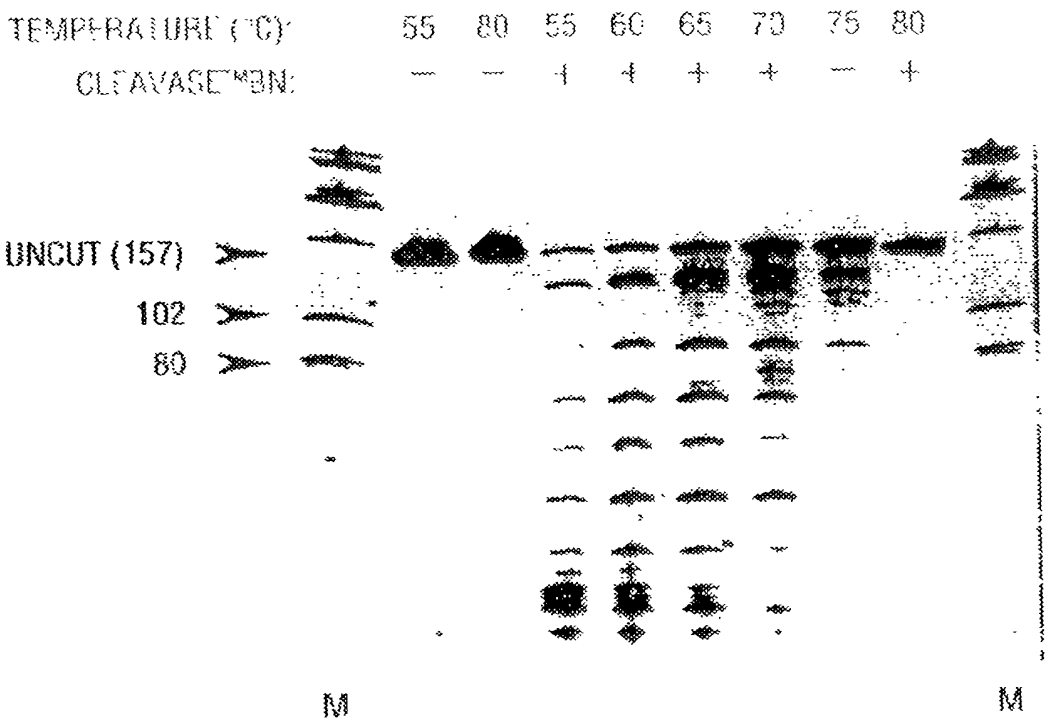

TEMPERATURE (°C):
55 80 55 60 65 70 75 80
CLEAVASE™BN:
— — + + + + — +
UNCUT (157)
102
80
M
M

FIG. 37

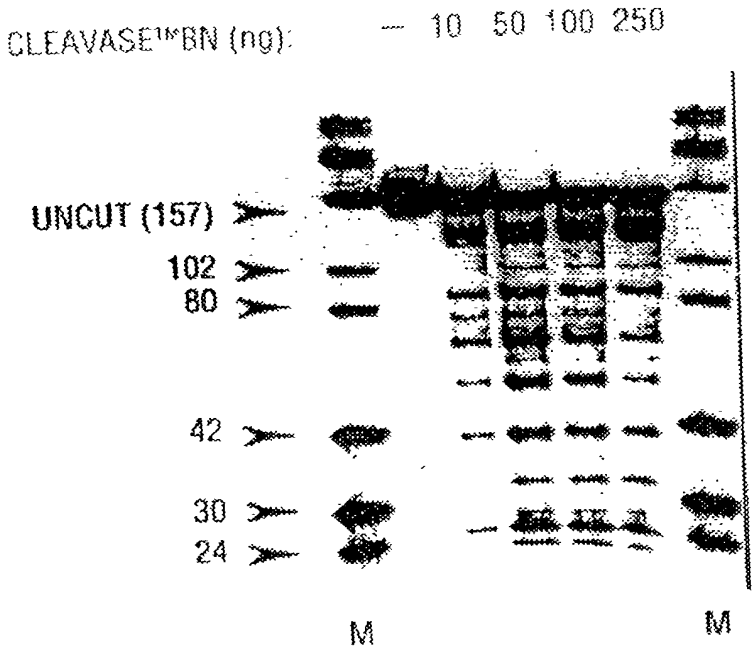


FIG. 38

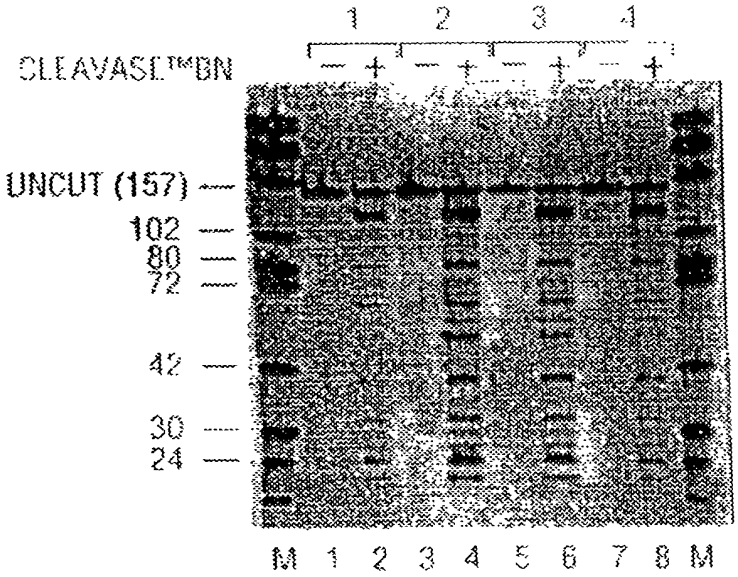


FIG. 39

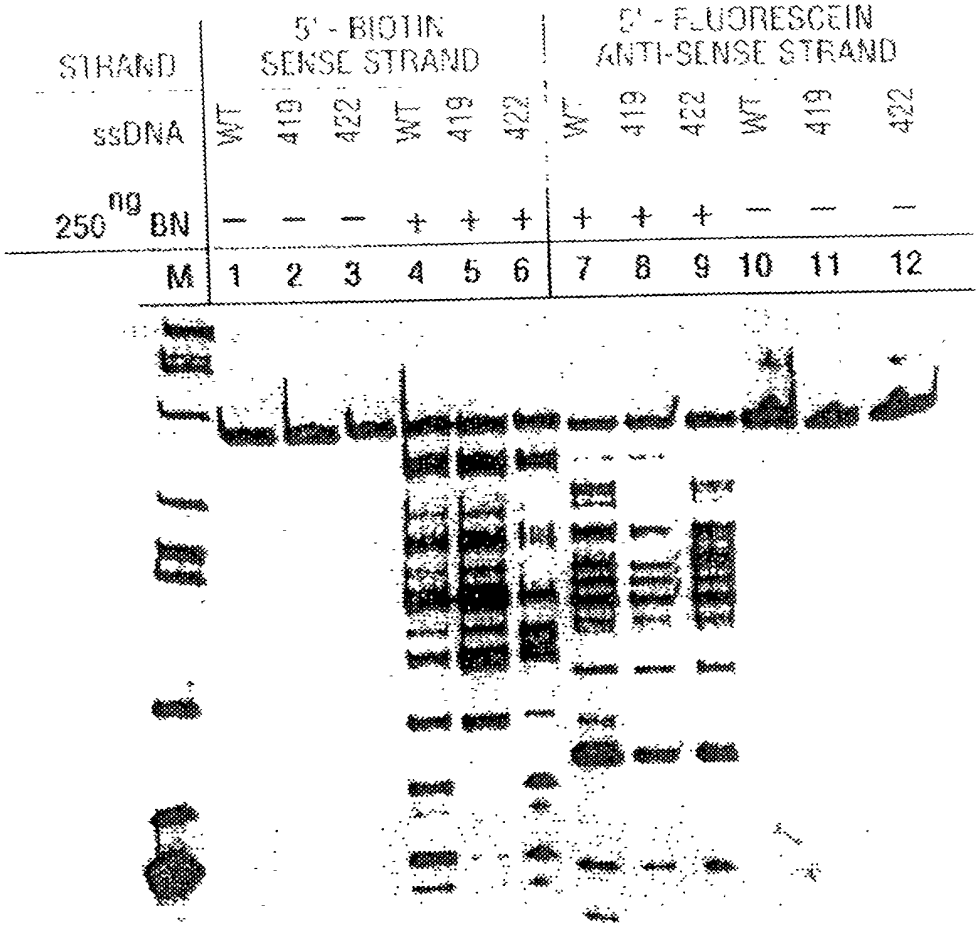

STRAND
5' - BIOTIN SENSE STRAND
5' - FLUORESCEIN ANTI-SENSE STRAND
ssDNA
WT
419
422
WT
419
422
WT
419
422
WT
419
422
250 ng BN
M
1 2 3 4 5 6 7 8 9 10 11 12

FIG. 40

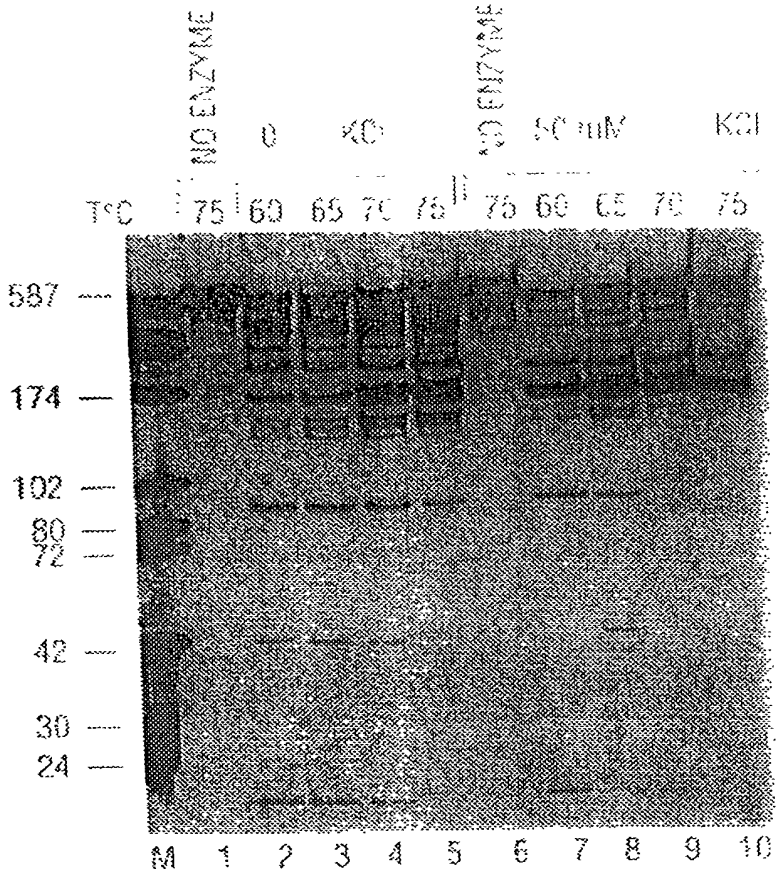

NO ENZYME
0
40
NO ENZYME
50 mM
KCl
T°C
75
60
65
70
75
75
60
65
70
75
587
174
102
80
72
42
30
24
M
1
2
3
4
5
6
7
8
9
10

FIG. 41

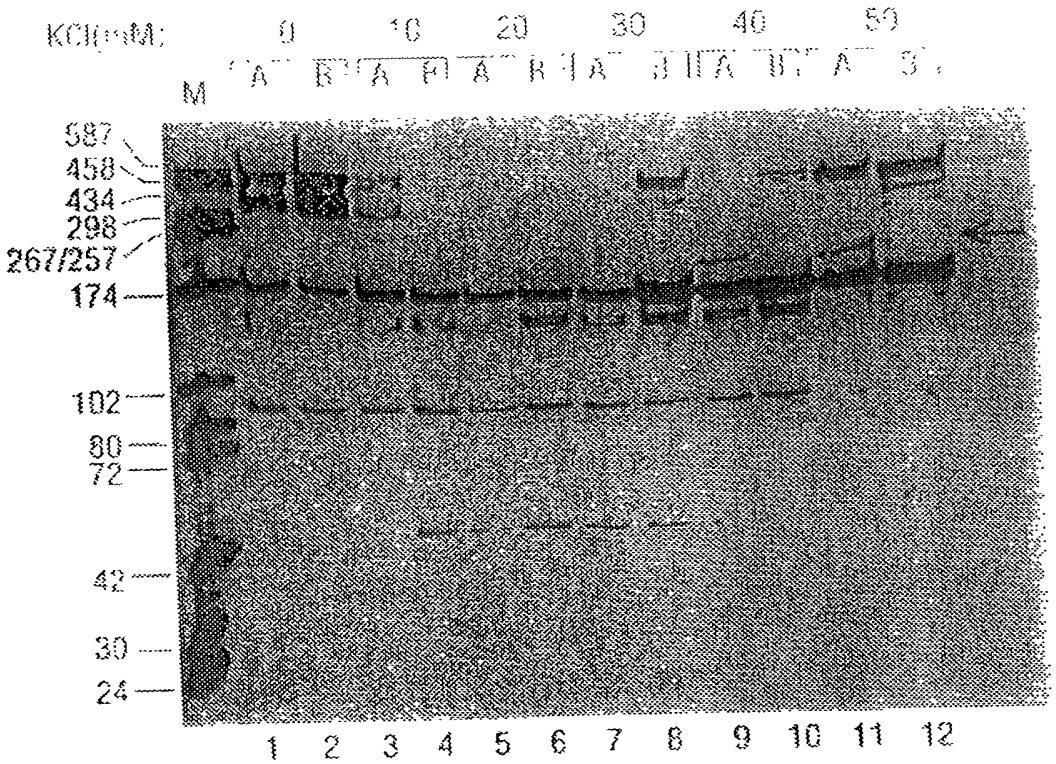

KCl(mM):
0
10
20
30
40
50
M
587
458
434
298
267/257
174
102
80
72
42
30
24
1 2 3 4 5 6 7 8 9 10 11 12

FIG. 42

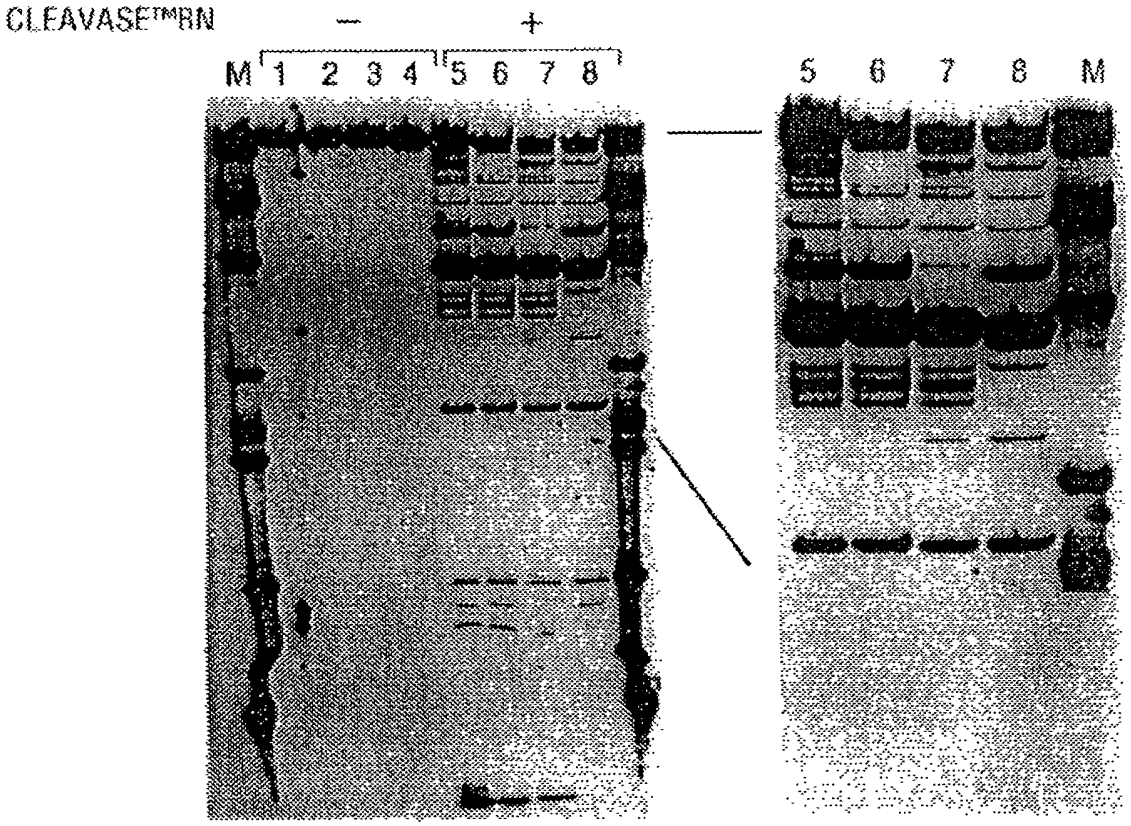


FIG. 43

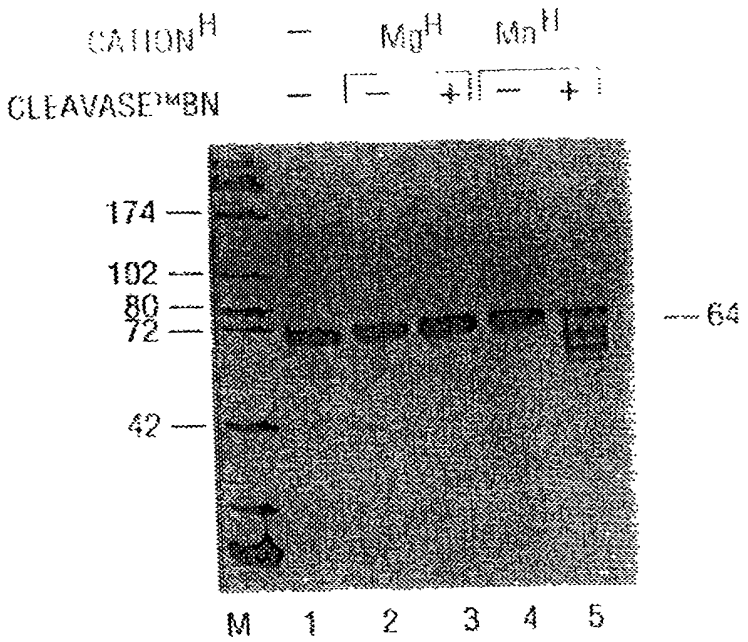


FIG. 44

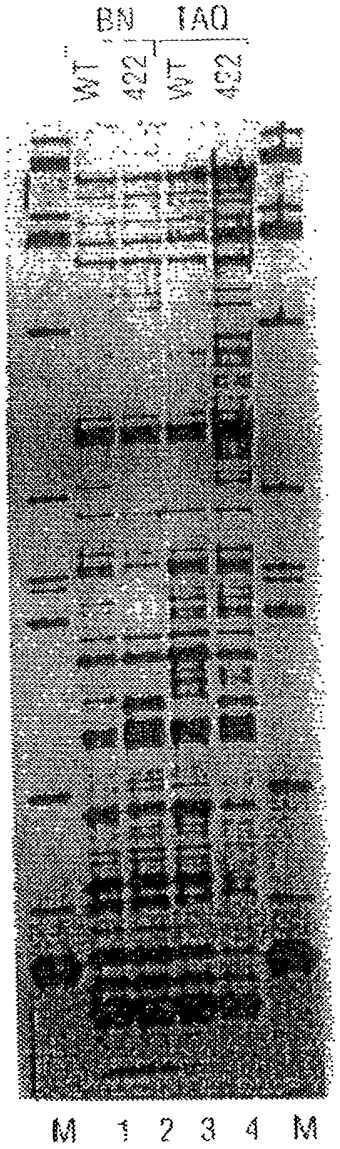


FIG. 45

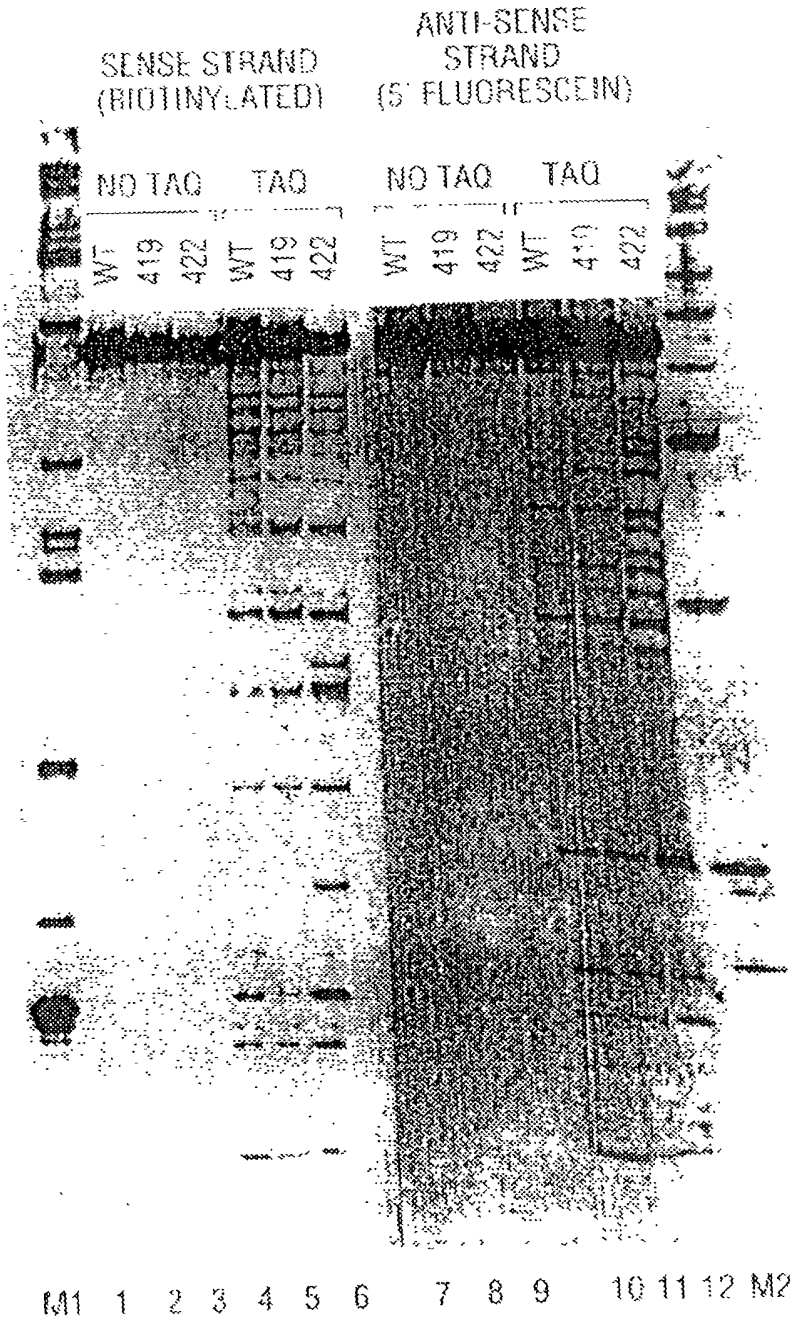

SENSE STRAND
(BIOTINYLATED)
ANTI-SENSE
STRAND
(5' FLUORESCEIN)
NO TAQ
TAQ
NO TAQ
TAQ
WT
419
422
WT
419
422
WT
419
422
WT
419
422
M1 1 2 3 4 5 6 7 8 9 10 11 12 M2

FIG. 46

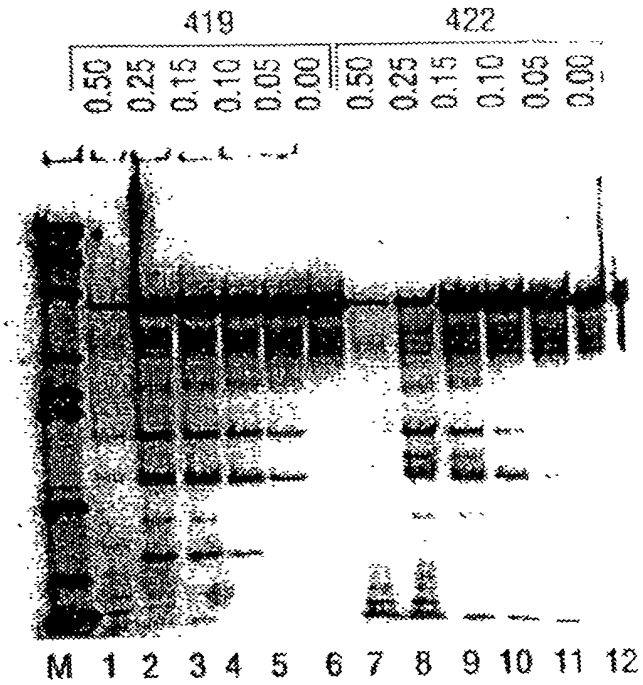

419
422
0.50
0.25
0.15
0.10
0.05
0.00
0.50
0.25
0.15
0.10
0.05
0.00
M 1 2 3 4 5 6 7 8 9 10 11 12

FIG. 47

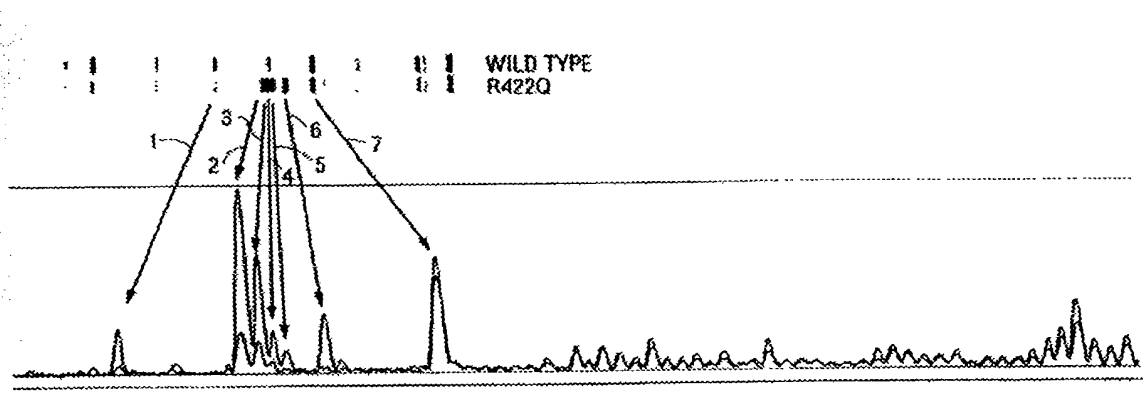


FIG. 48

```
                                                                        50
L.100.8-1           5'GGCTGACAAGAAGGAAACTCGCTGAGACAGCAGGGACTTTCCACAAGGGG
(SEQ ID NO: 76)     3'CCGACTGTTCTTCCTTTGAGCGACTCTGTCGTCCCTGAAAGGTGTTCCCC

L.46.16-10          5'GGCTGACAAGAAGGAAACTCGCTGAGATAGCAGGGACTTTCCACAAGGGG
(SEQ ID NO: 77)     3'CCGACTGTTCTTCCTTTGAGCGACTCTATCGTCCCTGAAAGGTGTTCCCC

L.46.16-12          5'GGCTGACAAGAAGGAAACTCGCTGAGATAGCAGGGACTTTCCACAAGGGG
(SEQ ID NO: 78)     3'CCGACTGTTCTTCCTTTGAGCGACTCTATCGTCCCTGAAAGGTGTTCCCC

L19.16-3            5'GGCTGACAAGAAGGAAACTCGCTGAGACAGCAGGGACTTTCCACAAGGGG
(SEQ ID NO: 79)     3'CCGACTGTTCTTCCTTTGAGCGACTCTGTCGTCCCTGAAAGGTGTTCCCC

L.CEM/251           5'GGCTGACAAGAAGGAAACTCGCTGAAACAGCAGGGACTTTCCACAAGGGG
(SEQ ID NO: 80)     3'CCGACTGTTCTTCCTTTGAGCGACTTTGTCGTCCCTGAAAGGTGTTCCCC

L.36.8-3            5'GGCTGACAAGAAGGAAACTCGCTGAGACAGCAGGGACTTTCCACAAGGGG
(SEQ ID NO: 81)     3'CCGACTGTTCTTCCTTTGAGCGACTCTGTCGTCCCTGAAAGGTGTTCCCC
```

FIG. 49A

```
                                                                  100
L.100.8-1          ATGTTACGGGGAGGTACTGGGGAGGAGCCGGTCGGGAACGCCCACTCTCT
(SEQ ID NO: 76)    TACAATGCCCCTCCATGACCCCTCCTCGGCCAGCCCTTGCGGGTGAGAGA

                   ATGTTATGGGGAGG-----------AGCCGGTCGGGAACACCCACTTTCT
L.46.16-10
(SEQ ID NO: 77)    TACAATACCCCTCC-----------TCGGCCAGCCCTTGTGGGTGAAAGA

                   ATGTTATGGGGAGG-----------AGCCGGTCGGGAACACCCACTTTCT
L.46.16-12
(SEQ ID NO: 78)    TACAATACCCCTCC-----------TCGGCCAGCCCTTGTGGGTGAAAGA

                   ATGTTACGGGGAGGTACTGGGGAGGAGCCGGTCGGGAACGCCCCCTCTCT
L19.16-3
(SEQ ID NO: 19)    TACAATGCCCCTCCATGACCCCTCCTCGGCCAGCCCTTGCGGGGGAGAGA

                   ATGTTACGGGGAGGTACTGGGAAGGAGCCGGTCGGGAACGCCCACTTTCT
L.CEM/251
(SEQ ID NO: 80)    TACAATGCCCCTCCATGACCCTTCCTCGGCCAGCCCTTGCGGGTGAAAGA

                   ATGTTACGGAGAGGTACTGGGGAGGAGCCGGTCGGGAACGCCCACTCTCT
L.36.8-3
(SEQ ID NO: 81)    TACAATGCCTCTCCATGACCCCTCCTCGGCCAGCCCTTGCGGGTGAGAGA
```

FIG. 49B

		150
L.100.8-1	5'TGATGTATAAATATCACTGCATTTCGCTCTGTATTCAGTCGCTCTGCGGA 3'ACTACATATTTATAGTGACGTAAAGCGAGACATAAGTCAGCGAGACGCCT	
L.46.16-10	5'TGATGTATAAATATCACTGCATTTCGCTCTGTATTCAGTCGCTCTGCGGA 3'ACTACATATTTATAGTGACGTAAAGCGAGACATAAGTCAGCGAGACGCCT	
L.46.16-12	5'TGGTGTATAAATATCACTGCATTTCGCTCTGTATTCAGTCGCTCTGCGGA 3'ACCACATATTTATAGTGACGTAAAGCGAGACATAAGTCAGCGAGACGCCT	
L.19.16-3	5'TGATGTATAAATATCACTGCATTTCGCTCTGTATTCAGTCGCTCTGCGGA 3'ACTACATATTTATAGTGACGTAAAGCGAGACATAAGTCAGCGAGACGCCT	
L.CEM/251	5'TGATGTATAAATATCACTGCATTTCGCTCTGTATTCAGTCGCTCTGCGGA 3'ACTACATATTTATAGTGACGTAAAGCGAGACATAAGTCAGCGAGACGCCT	
L.36.8-3	5'TGATGTATAAATATCACTGCATTTCGCTCTGTATTCAGTCGCTCTGCGGA 3'ACTACATATTTATAGTGACGTAAAGCGAGACATAAGTCAGCGAGACGCCT	

FIG. 49C

200

L.100.8-1	GAGGCTGGCAGATTGAGCCCTGGGAGGTTCTCTCCAGCACTAGCAGGTAG
	CTCCGACCGTCTAACTCGGGACCCTCCAAGAGAGGTCGTGATCGTCCATC
L.46.16-10	GAGGCTGGCAGATTGAGCCCTGGGAGGTTCTCTCCAGCACTAGCAGCTAG
	CTCCGACCGTCTAACTCGGGACCCTCCAAGAGAGGTCGTGATCGTCCATC
L.46.16-12	GAGGCTGGCAGATTGAGCCCTGGGAGGTTCTCTCCAGCACTAGCAGGTAG
	CTCCGACCGTCTAACTCGGGACCCTCCAAGAGAGGTCGTGATCGTCCATC
L.19.16-3	GAGGCTGGCAGATTGAGCCCTGGGAGGTTCTCTCCAGCACTAGCAGGTAG
	CTCCGACCGTCTAACTCGGGACCCTCCAAGAGAGGTCGTGATCGTCCATC
L.CEM/251	GAGGCTGGCAGATTGAGCCCTGGGAGGTTCTCTCCAGCACTAGCAGGTAG
	CTCCGACCGTCTAACTCGGGACCCTCCAAGAGAGGTCGTGATCGTCCATC
L.36.8-3	GAGGCTGGCAGATTGAGCCCTAGGAGGTTCTCTCCAGCACTAGCAGGTAG
	CTCCGACCGTCTAACTCGGGATCCTCCAAGAGAGGTCGTGATCGTCCATC

FIG. 49D

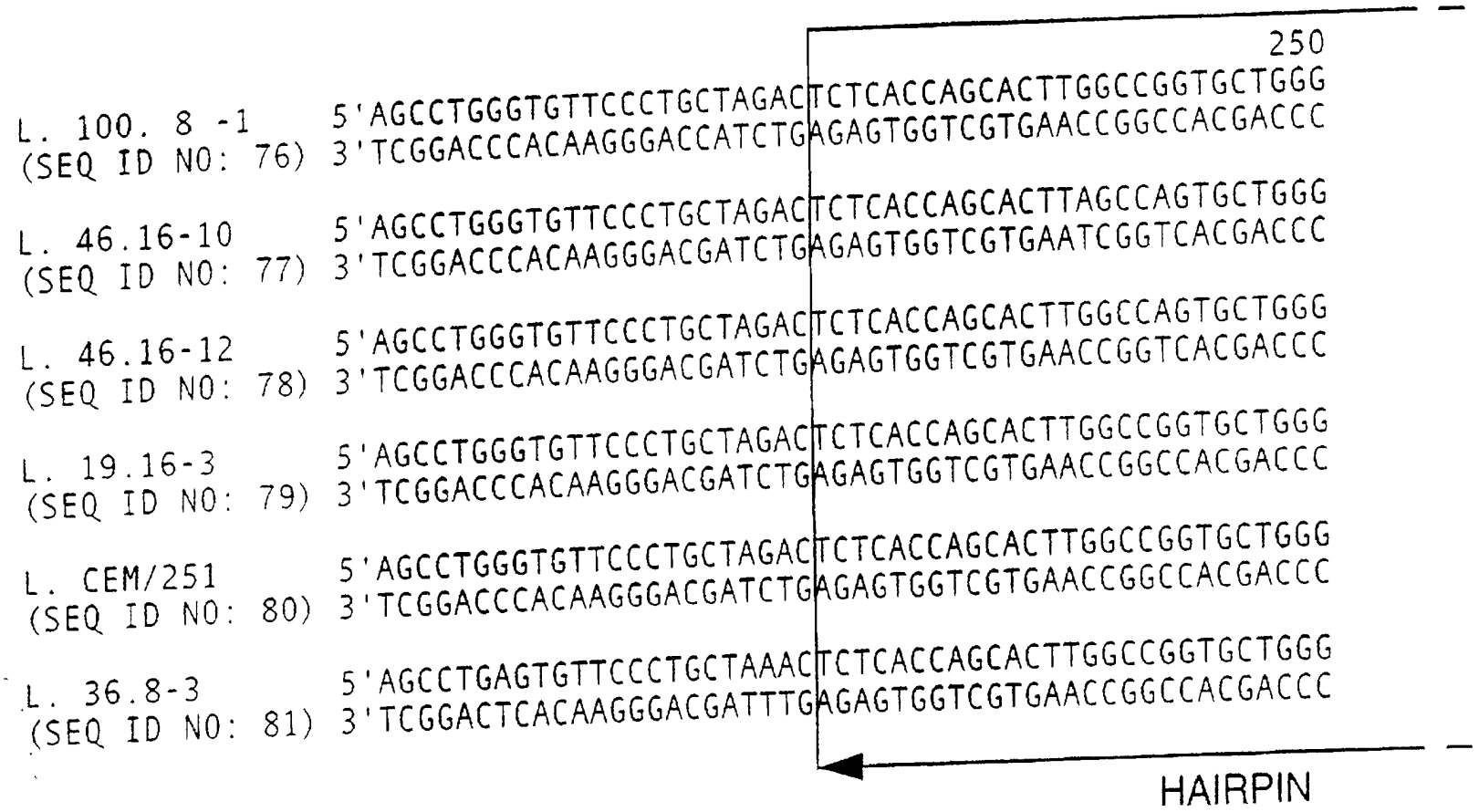

250
L. 100. 8 -1
(SEQ ID NO: 76)
5'AGCCTGGGTGTTCCCTGCTAGACTCTCACCAGCACTTGGCCGGTGCTGGG
3'TCGGACCCACAAGGGACCATCTGAGAGTGGTCGTGAACCGGCCACGACCC
L. 46.16-10
(SEQ ID NO: 77)
5'AGCCTGGGTGTTCCCTGCTAGACTCTCACCAGCACTTAGCCAGTGCTGGG
3'TCGGACCCACAAGGGACGATCTGAGAGTGGTCGTGAATCGGTCACGACCC
L. 46.16-12
(SEQ ID NO: 78)
5'AGCCTGGGTGTTCCCTGCTAGACTCTCACCAGCACTTGGCCAGTGCTGGG
3'TCGGACCCACAAGGGACGATCTGAGAGTGGTCGTGAACCGGTCACGACCC
L. 19.16-3
(SEQ ID NO: 79)
5'AGCCTGGGTGTTCCCTGCTAGACTCTCACCAGCACTTGGCCGGTGCTGGG
3'TCGGACCCACAAGGGACGATCTGAGAGTGGTCGTGAACCGGCCACGACCC
L. CEM/251
(SEQ ID NO: 80)
5'AGCCTGGGTGTTCCCTGCTAGACTCTCACCAGCACTTGGCCGGTGCTGGG
3'TCGGACCCACAAGGGACGATCTGAGAGTGGTCGTGAACCGGCCACGACCC
L. 36.8-3
(SEQ ID NO: 81)
5'AGCCTGAGTGTTCCCTGCTAAACTCTCACCAGCACTTGGCCGGTGCTGGG
3'TCGGACTCACAAGGGACGATTTGAGAGTGGTCGTGAACCGGCCACGACCC
HAIRPIN

FIG. 49E

		300
L. 100. 8 -1 (SEQ ID NO: 76)	CAGAGTG	GCTCCACGCTTGCTTGCTTAAAGACCTCTTCAATAAAGCTGCC
	GTCTCAC	CGAGGTGCGAACGAACGAATTTCTGGAGAAGTTATTTCGACGC
L. 46.16-10 (SEQ ID NO: 77)	CAGAGTG	GCTCCACGCTTGCTTGCTTAAAGACCTCTTCAATAAAGCTGCC
	GTCTCAC	CGAGGTGCGAACGAACGAATTTCTGGAGAAGTTATTTCGACGG
L. 46.16-12 (SEQ ID NO: 78)	CAGAGTG	GCTCCACGCTTGCTTGCTTAAAGACCTCTTCAATAAAGCTGCC
	GTCTCAC	CGAGGTGCGAACGAACGAATTTCTGGAGAAGTTATTTCGACGG
L. 19.16-3 (SEQ ID NO: 79)	CAGAGTG	GCTCCACGCTTGCTTGCTTAAAGACCTCTTCAATAAAGCTGCC
	GTCTCAC	CGAGGTGCGAACGAACGAATTTCTGGAGAAGTTATTTCGACGG
L. CEM/251 (SEQ ID NO: 80)	CAGAGTG	ACTCCACGCTTGCTTGCTTAAAGCCCTCTTCAATAAAGCTGCC
	GTCTCAC	TGAGGTGCGAACGAACGAATTTCGGGAGAAGTTATTTCGACGG
L. 36.8-3 (SEQ ID NO: 81)	CAGAGCG	GCTCCACGCTTGCTTGCTTAAAGACCTCTTCAATAAAGCTGCC
	GTCTCGC	CGAGGTGCGAACGAACGAATTTCTGGAGAAGTTATTTCGACGG

HAIRPIN

FIG. 49F

09940925 .022602

	350	
L.100.8-1	5'ATTTTAGAAGTAGGCCAGTGTGTGTTCCCATCTCTCCTAGCCGCCGCCTG	G 3'
	3'TAAAATCTTCATCCGGTCACACACAAGGGTAGAGAGGATCGGCGGCGGAC	C 5'
L.46.16-10	5'ATTTTAGAAGTAAGCCAGTGTGTGTTCCCATCTCTCCTAGCCGCCGCCTG	G 3'
	3'TAAAATCTTCATTCGGTCACACACAAGGGTAGAGAGGATCGGCGGCGGAC	C 5'
L.46.16-12	5'ATTTTAGAAGTAAGCCAGTGTGTGTTCCCATCTCTCCTAGCCGCCGCCTG	G 3'
	3'TAAAATCTTCATTCGGTCACACACAAGGGTAGAGAGGATCGGCGGCGGAC	C 5'
L.19.16-3	5'ATTTTAGAAGTAGGCTAGTGTGTGTTCCCATCTCTCCTAGCCGCCGCCTG	G 3'
	3'TAAAATCTTCATCCGATCACACACAAGGGTAGAGAGGATCGGCGGCGGAC	C 5'
L.CEM/251	5'ATTTTAGAAGTAAGCTAGTGTGTGTTCCCATCTCTCCTAGCCGCCGCCTG	G 3'
	3'TAAAATCTTCATTCGATCACACACAAGGGTAGAGAGGATCGGCGGCGGAC	C 5'
L.36.8-3	5'ATTTTAGAAGTAGGCTAGTGTGTGTTCCCATCTCTCCTAGCCGCCGCCTG	G 3'
	3'TAAAATCTTCATCCGATCACACACAAGGGTAGAGAGGATCGGCGGCGGAC	C 5'

FIG. 49G

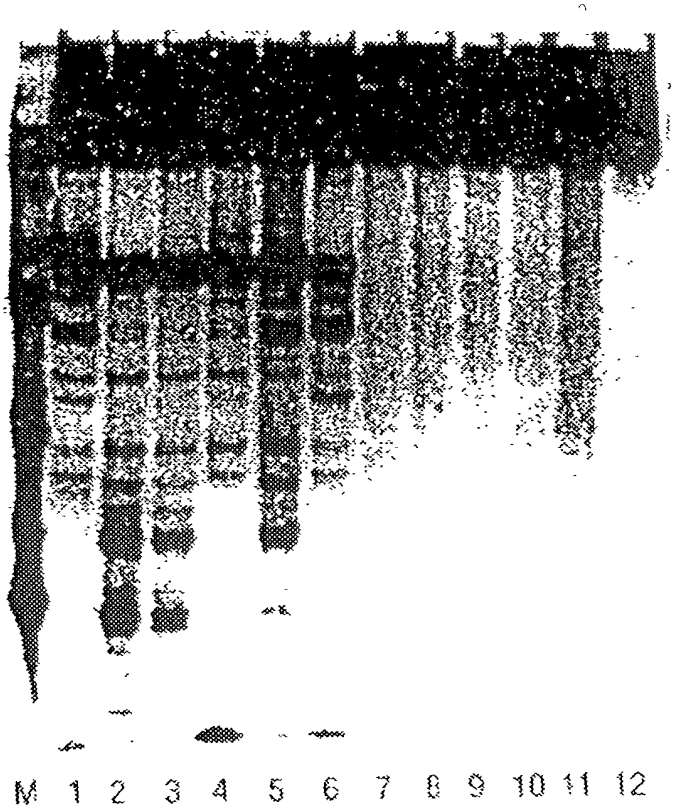


FIG. 50

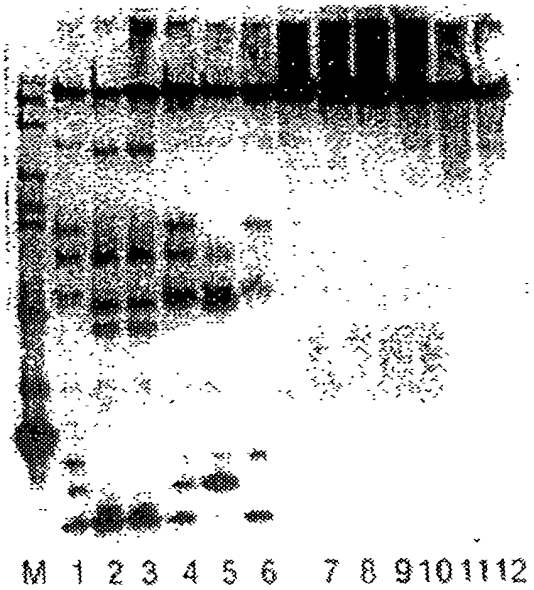


FIG. 51

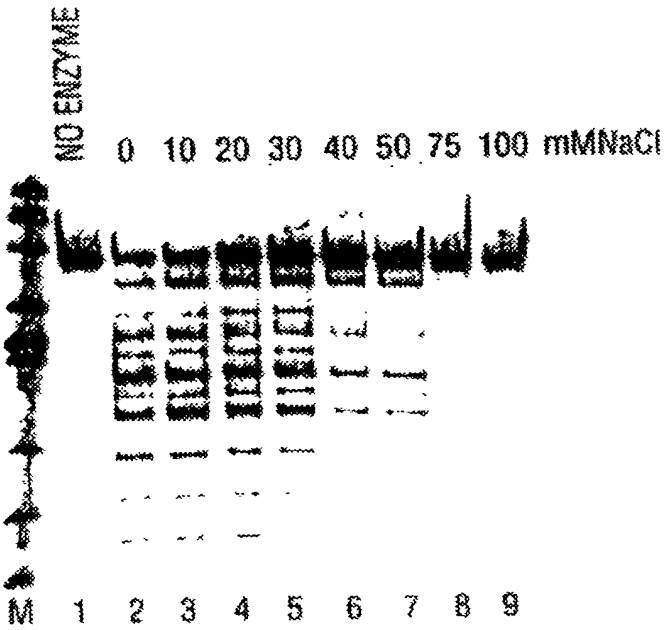


FIG. 52

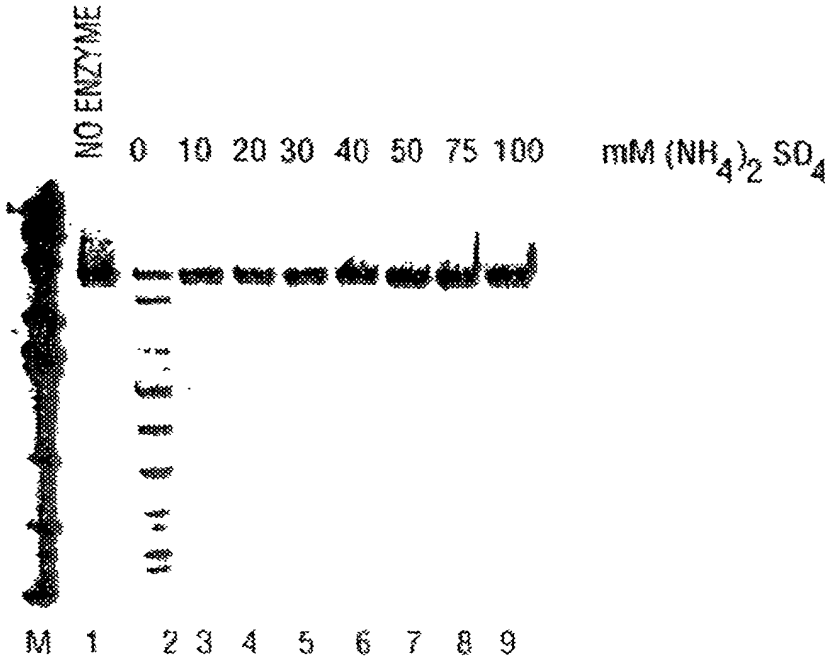


FIG. 53

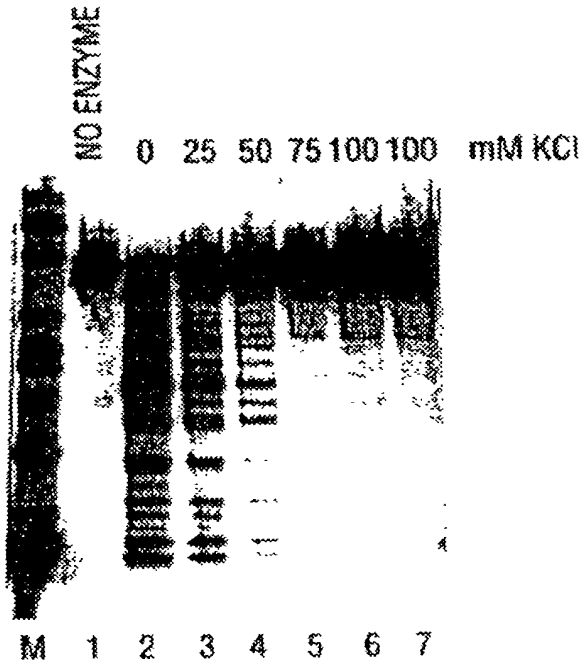


FIG. 54

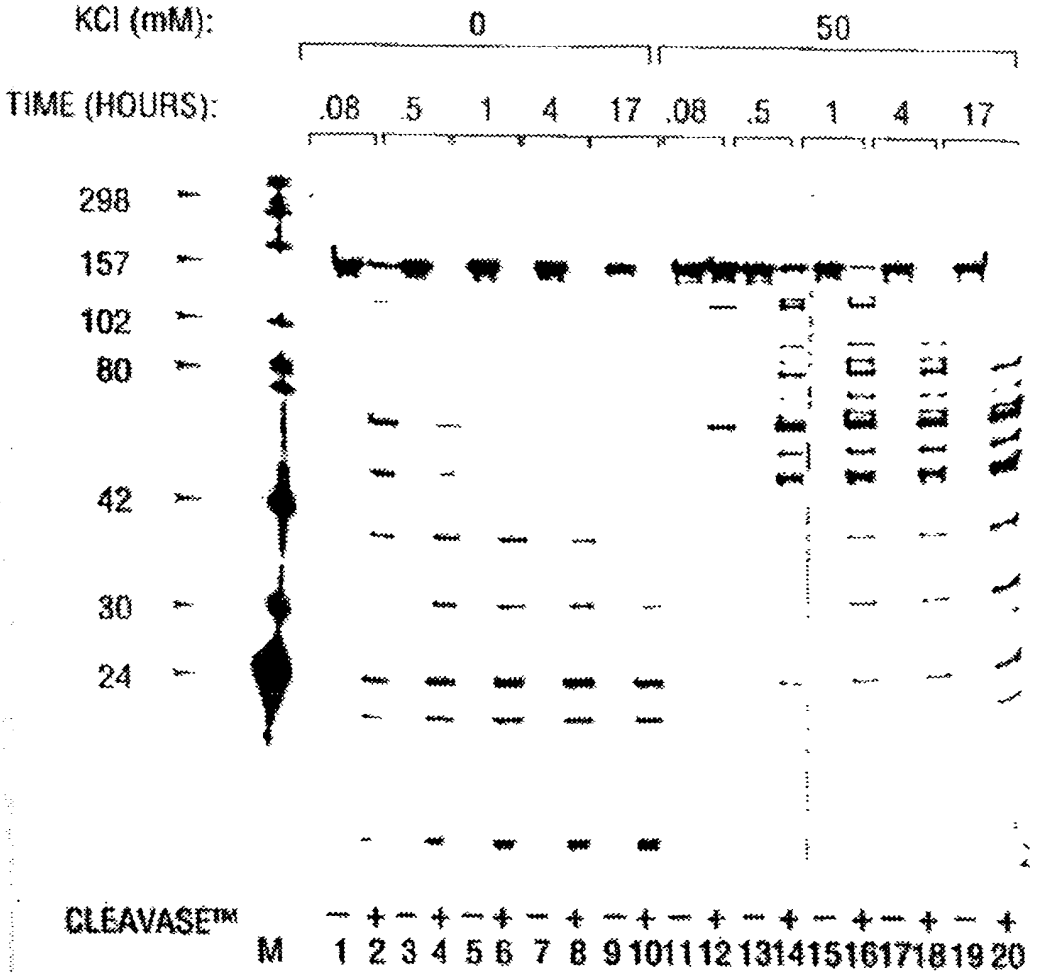

KCl (mM):
0
50
TIME (HOURS):
.08 .5 1 4 17 .08 .5 1 4 17
298
157
102
80
42
30
24
CLEAVASE™
M
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

FIG. 55

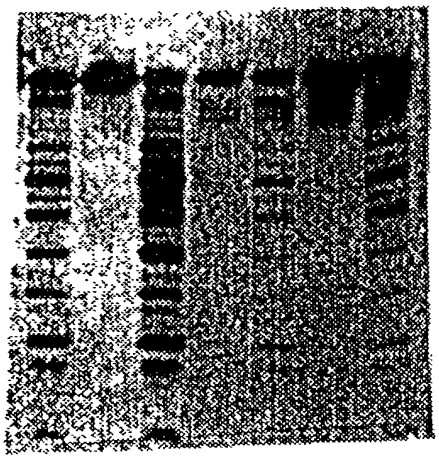


FIG. 56

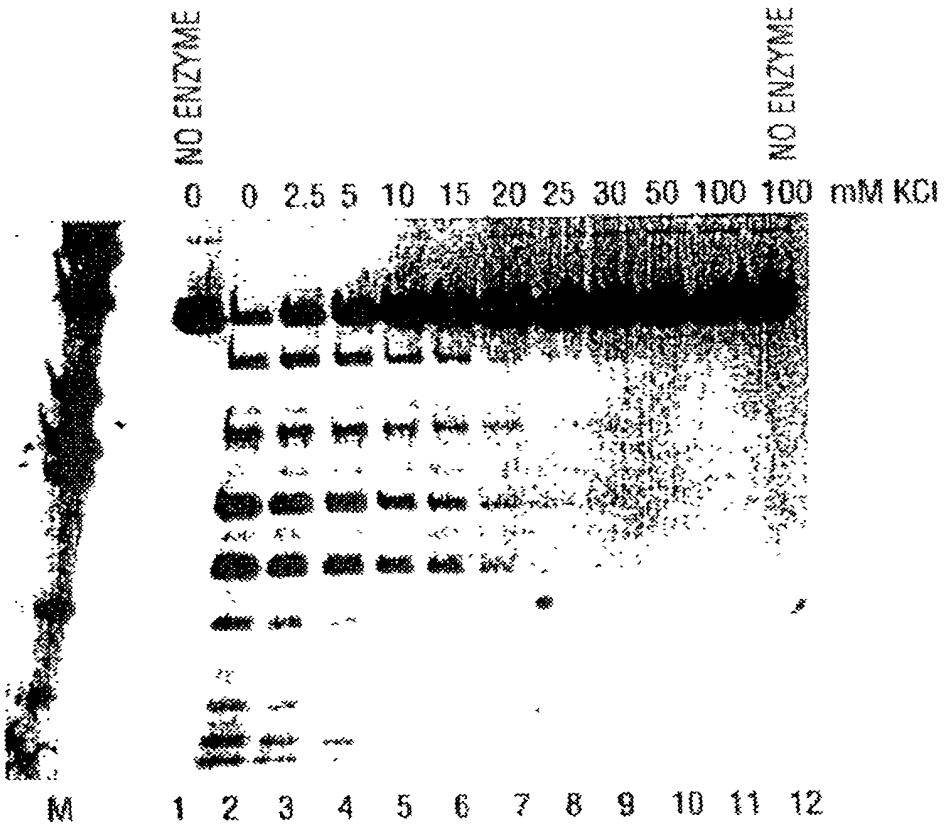

NO ENZYME
NO ENZYME
0 0 2.5 5 10 15 20 25 30 50 100 100 mM KCl
M 1 2 3 4 5 6 7 8 9 10 11 12

FIG. 57

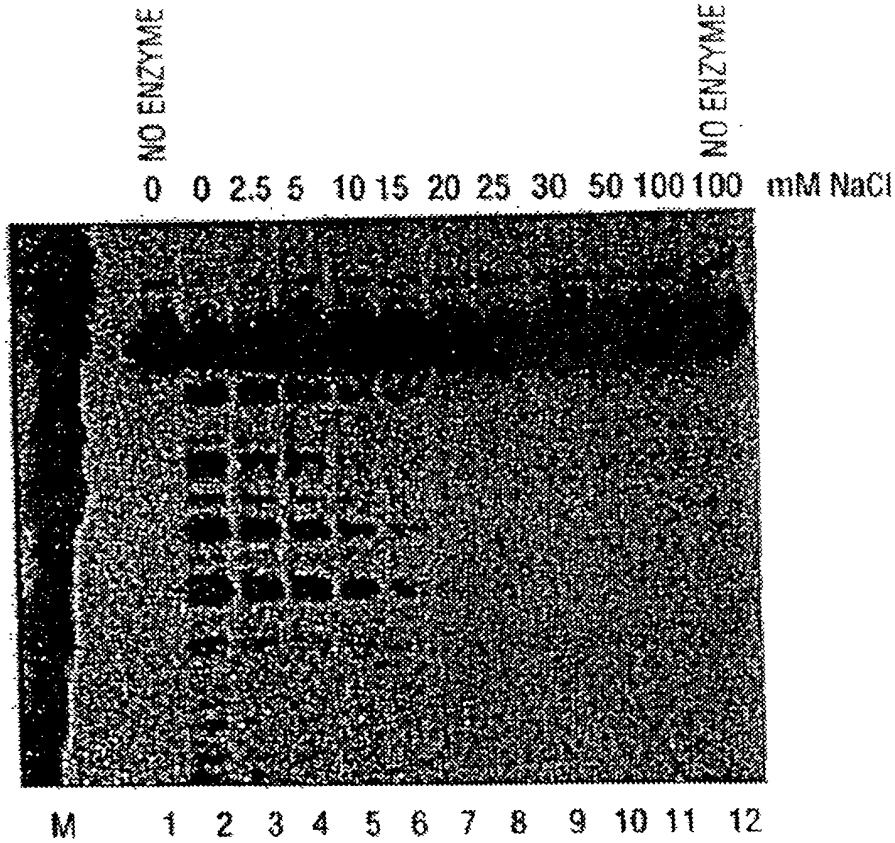

NO ENZYME
NO ENZYME
0 0 2.5 5 10 15 20 25 30 50 100 100 mM NaCl
M 1 2 3 4 5 6 7 8 9 10 11 12

FIG. 58

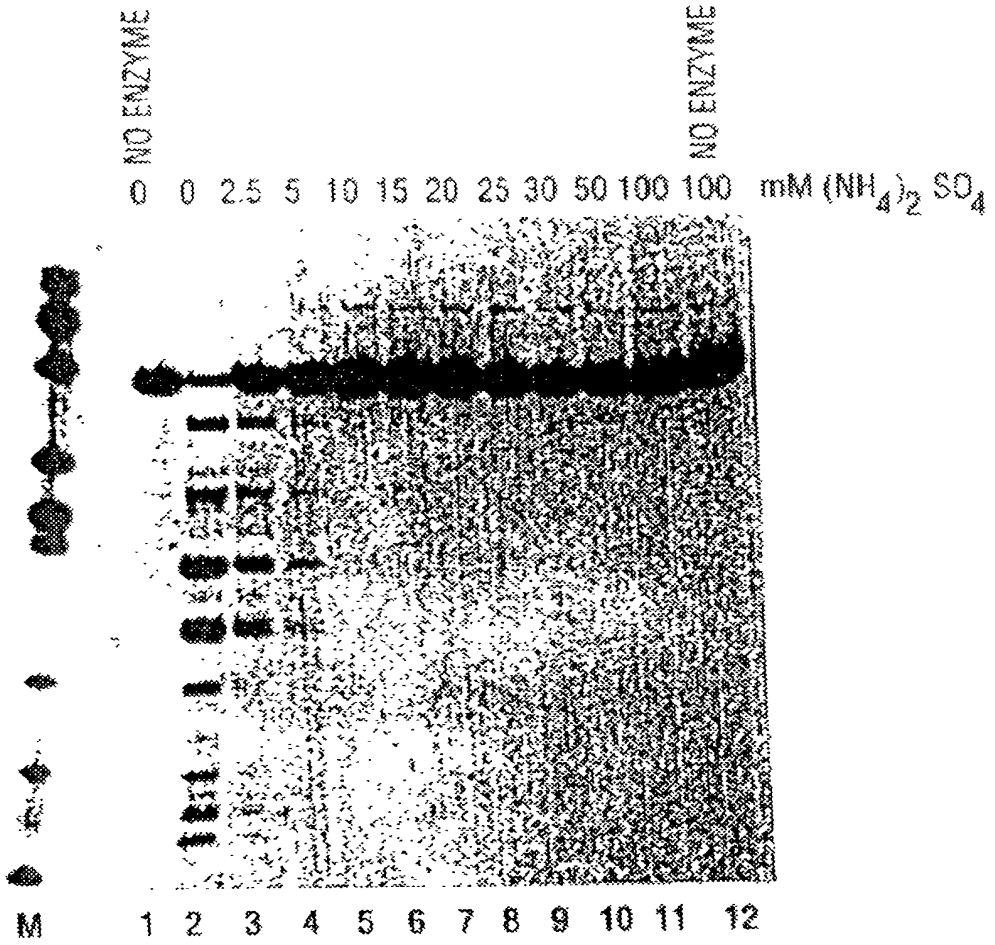

NO ENZYME
NO ENZYME
0 0 2.5 5 10 15 20 25 30 50 100 100 mM $(NH_4)_2$ SO_4
M 1 2 3 4 5 6 7 8 9 10 11 12

FIG. 59

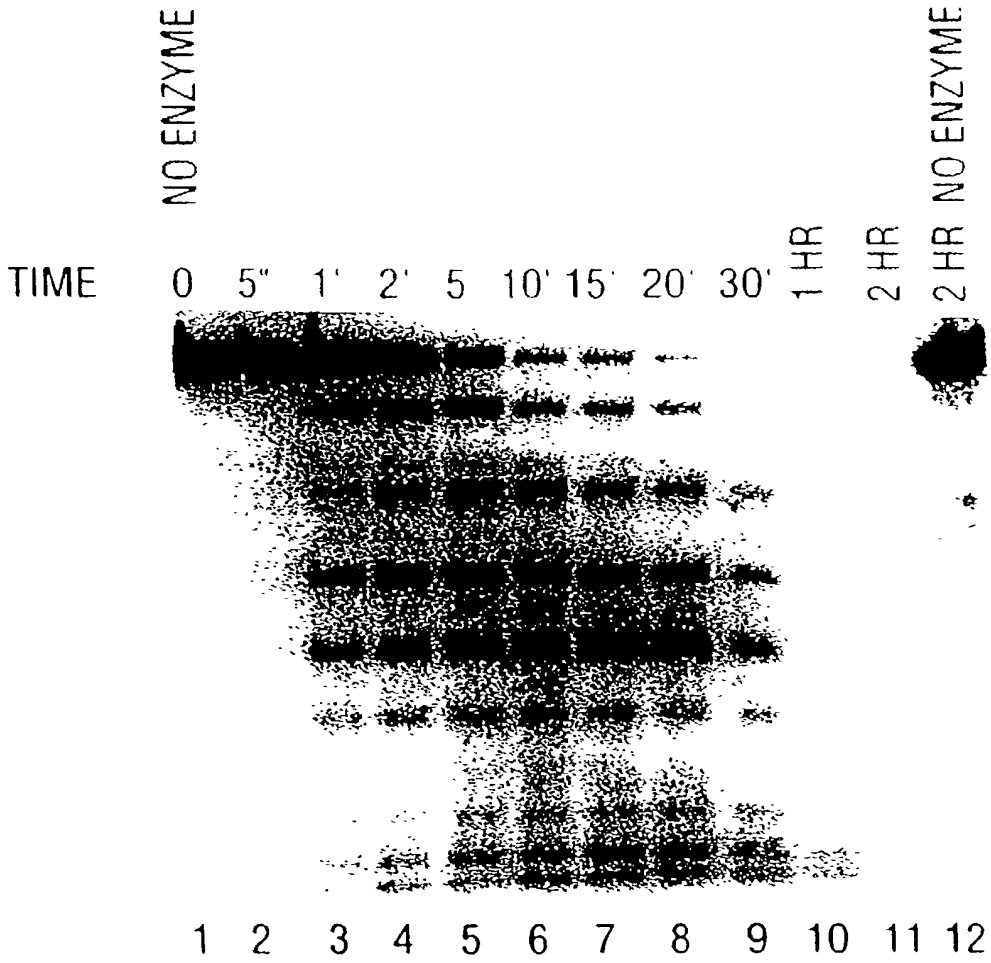

NO ENZYME
TIME
0
5'
1'
2'
5
10'
15'
20'
30'
1 HR
2 HR
2 HR
NO ENZYME
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 60

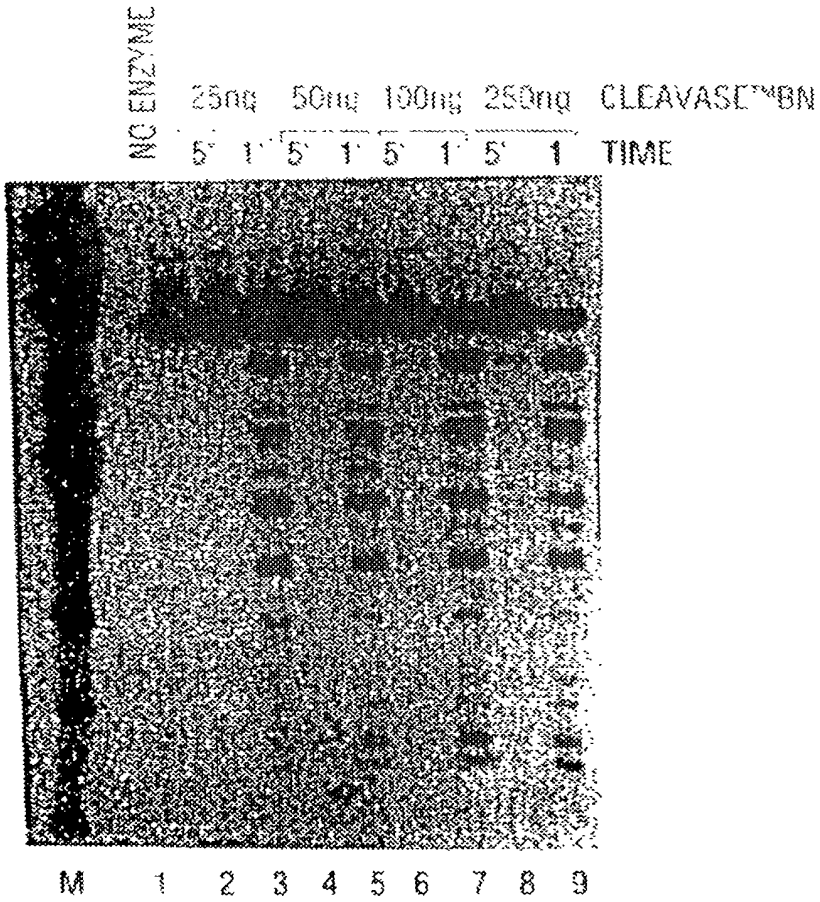

NO ENZYME
25ng
50ng
100ng
250ng
CLEAVASE™BN
5' 1' 5' 1' 5' 1' 5' 1'
TIME
M 1 2 3 4 5 6 7 8 9

FIG. 61

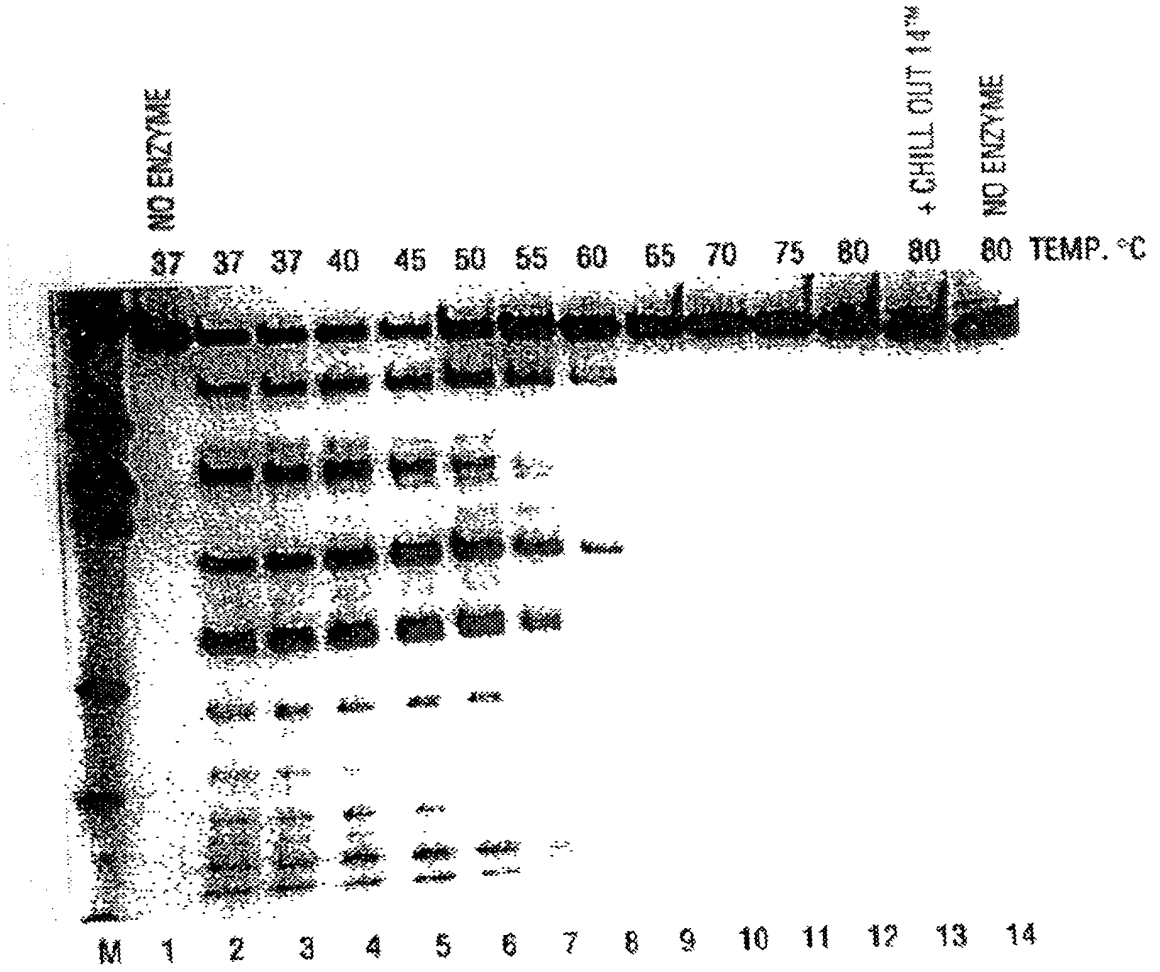

NO ENZYME
37 37 37 40 45 50 55 60 65 70 75 80 80 80 TEMP. °C
+ CHILL OUT 14™
NO ENZYME
M 1 2 3 4 5 6 7 8 9 10 11 12 13 14

FIG. 62

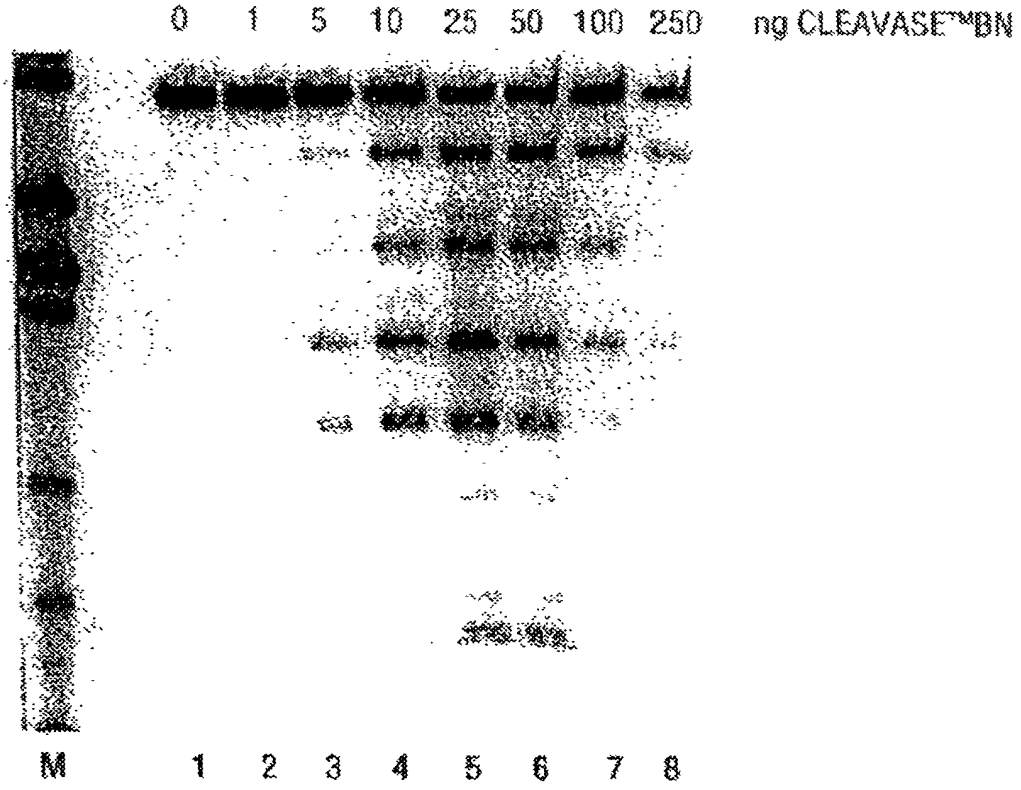


FIG. 63

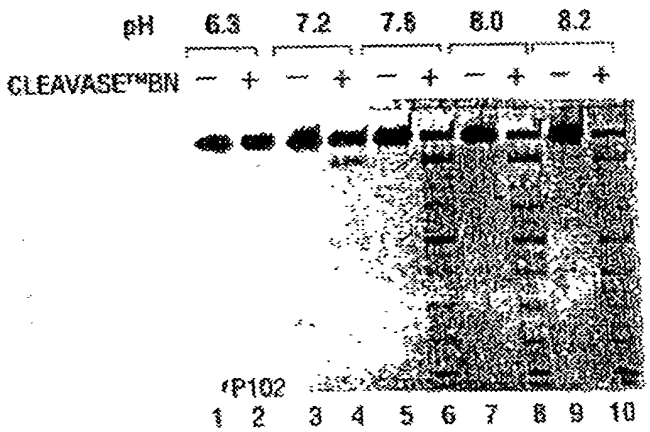


FIG. 64A

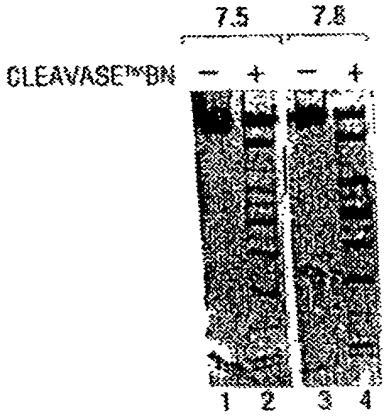


FIG. 64B

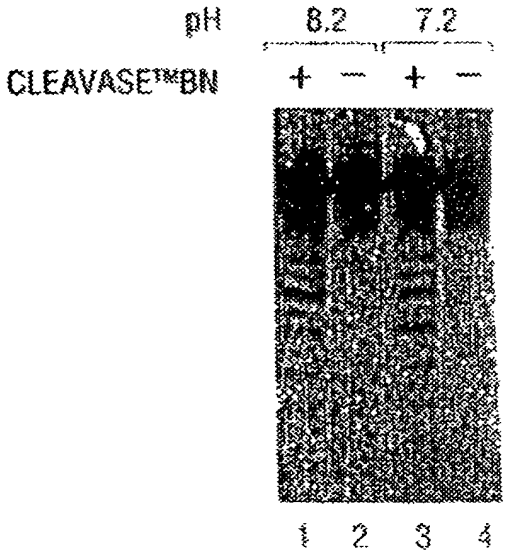


FIG. 65A

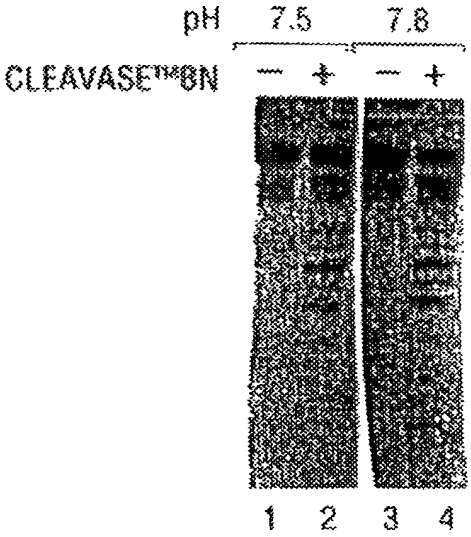


FIG. 65B

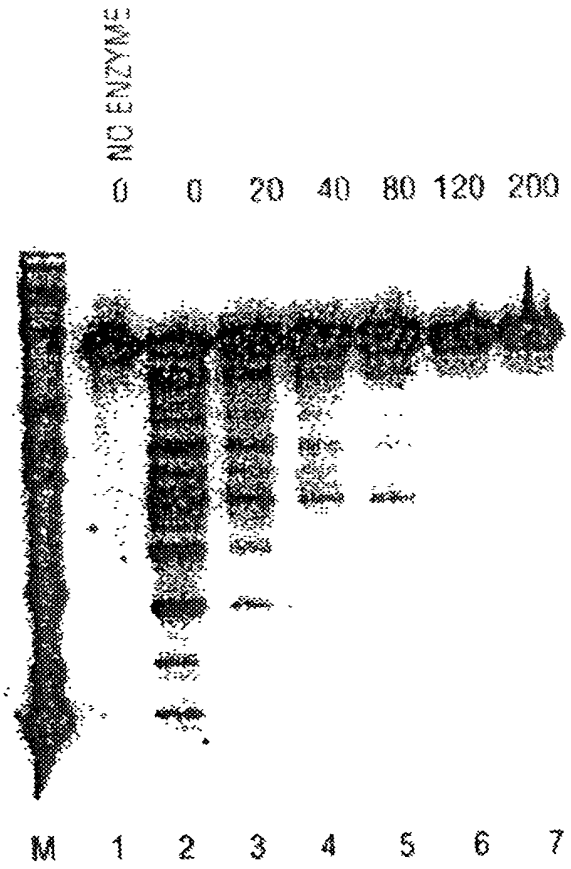


FIG. 66

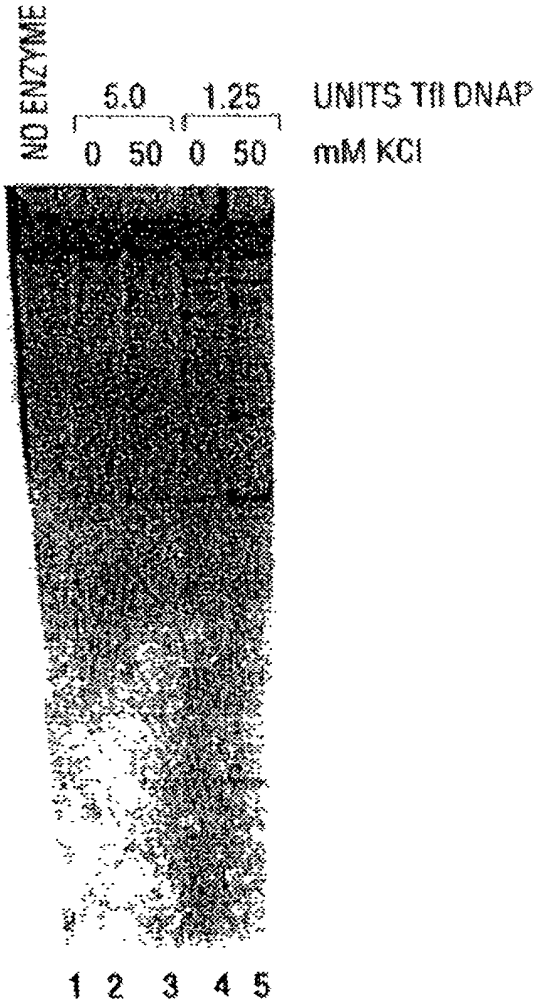


FIG. 67

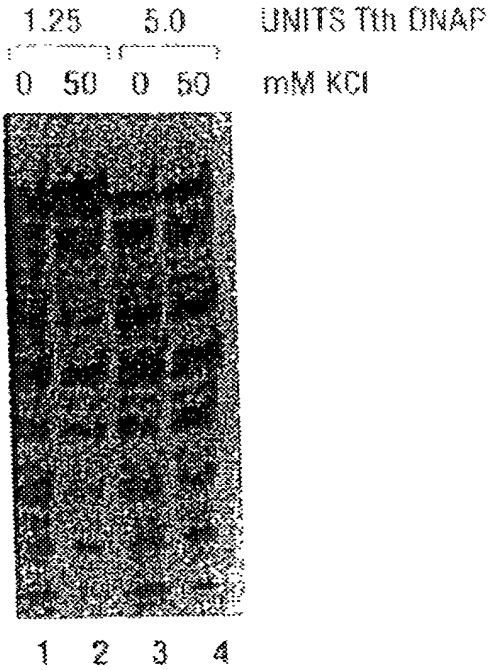


FIG. 68

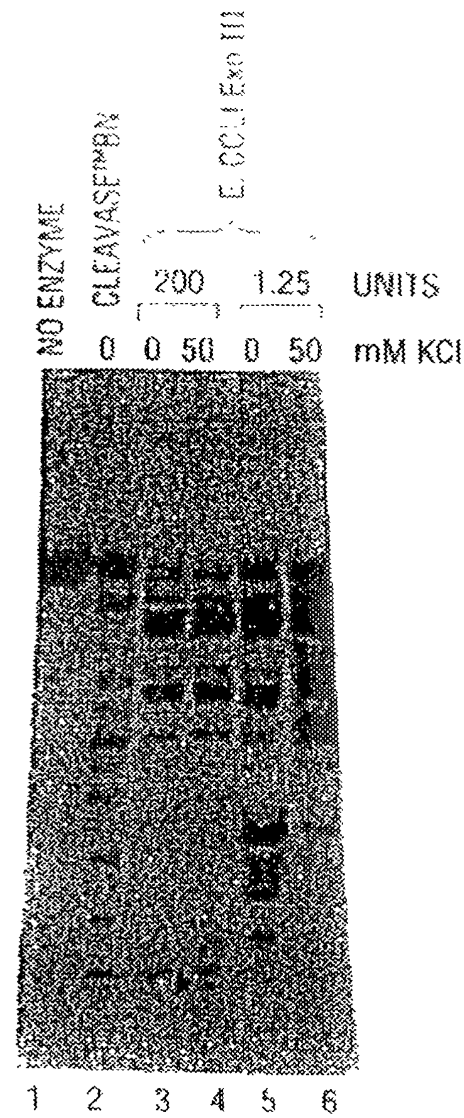

NO ENZYME
CLEAVASE™BN
E. COLI Exo III
200
1.25
UNITS
0
0
50
0
50
mM KCl
1
2
3
4
5
6

FIG. 69

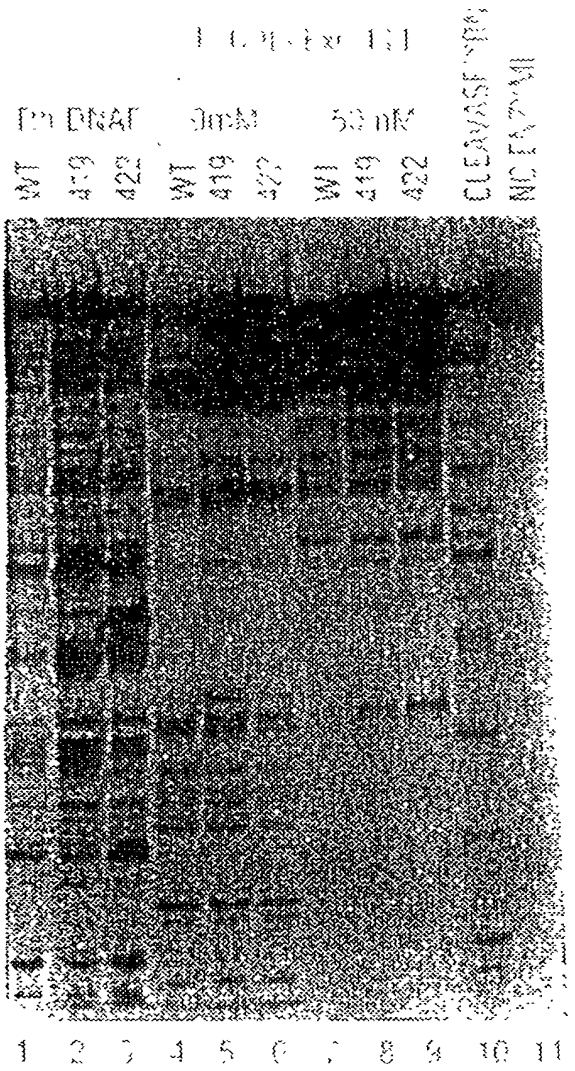
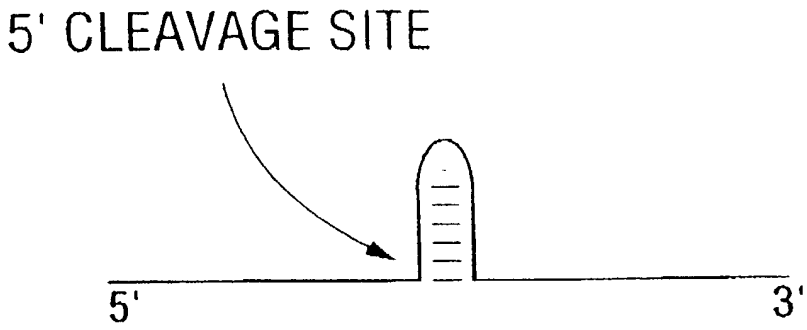


FIG. 70



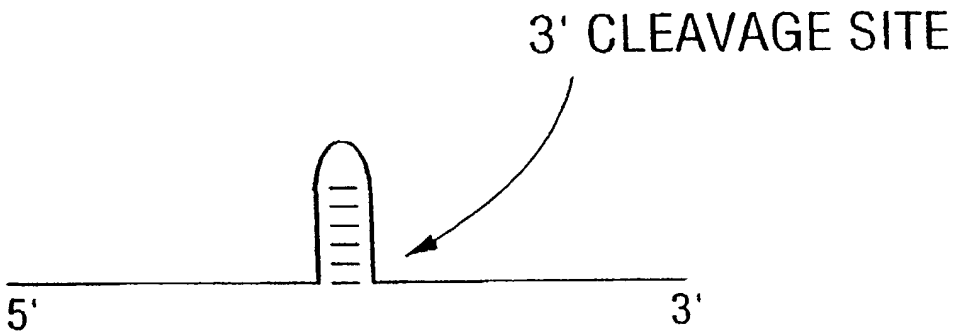


FIG. 71

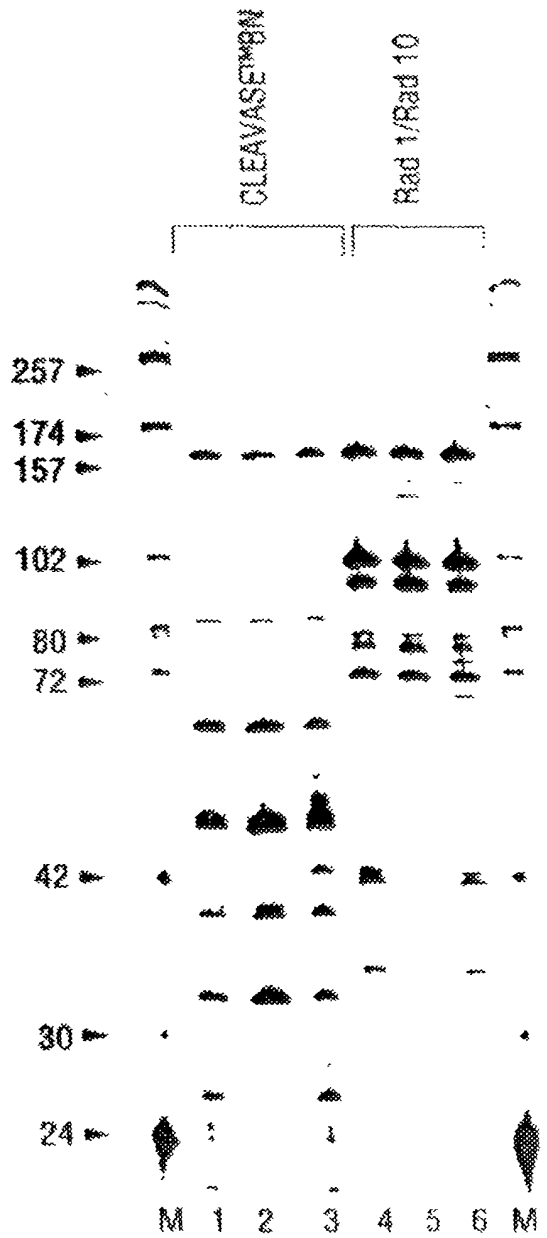


FIG. 72

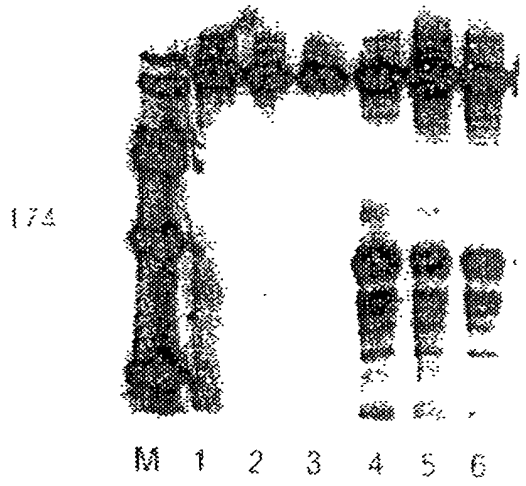


FIG. 73

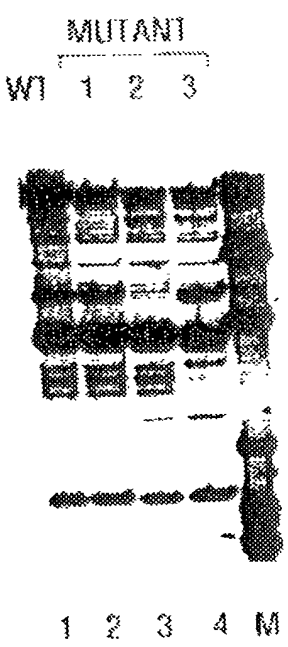


FIG. 74A

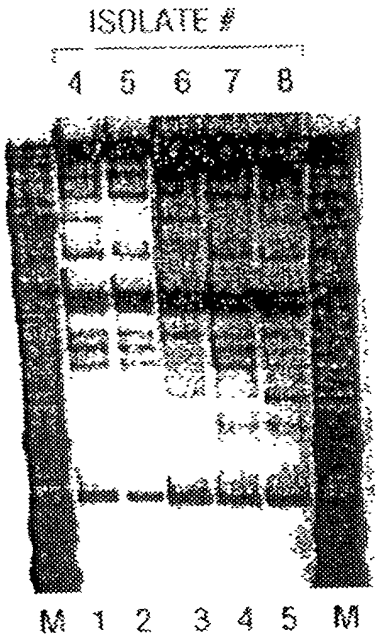


FIG. 74B

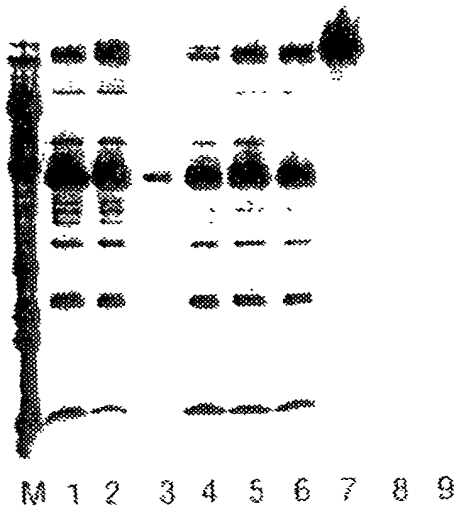


FIG. 75

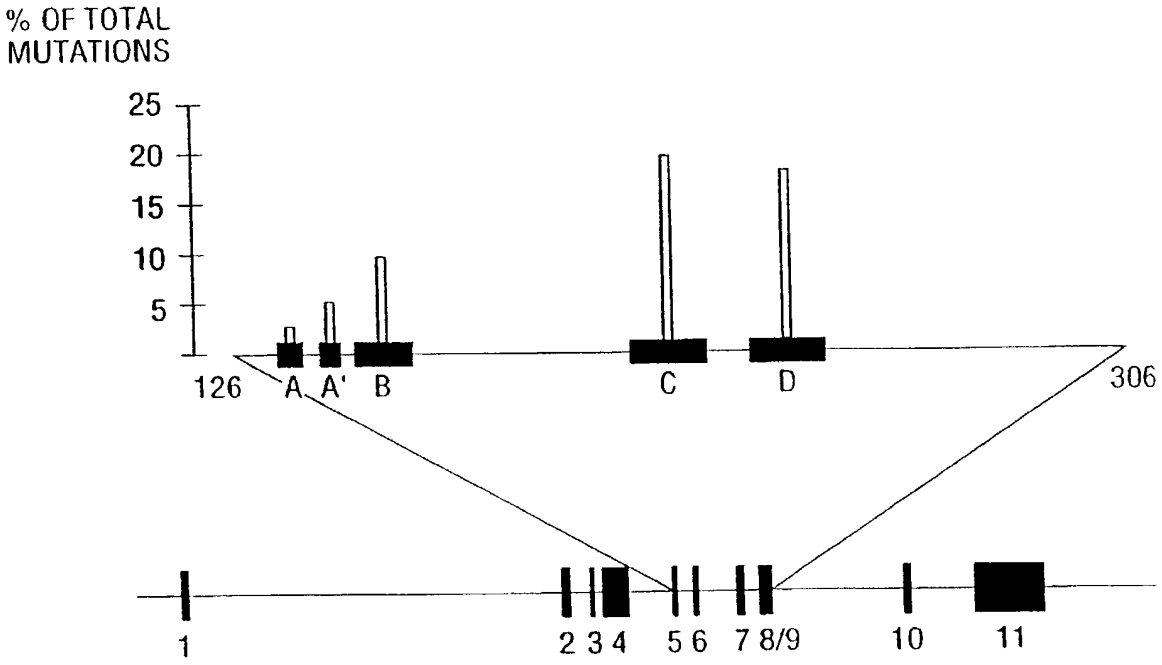


FIG. 76

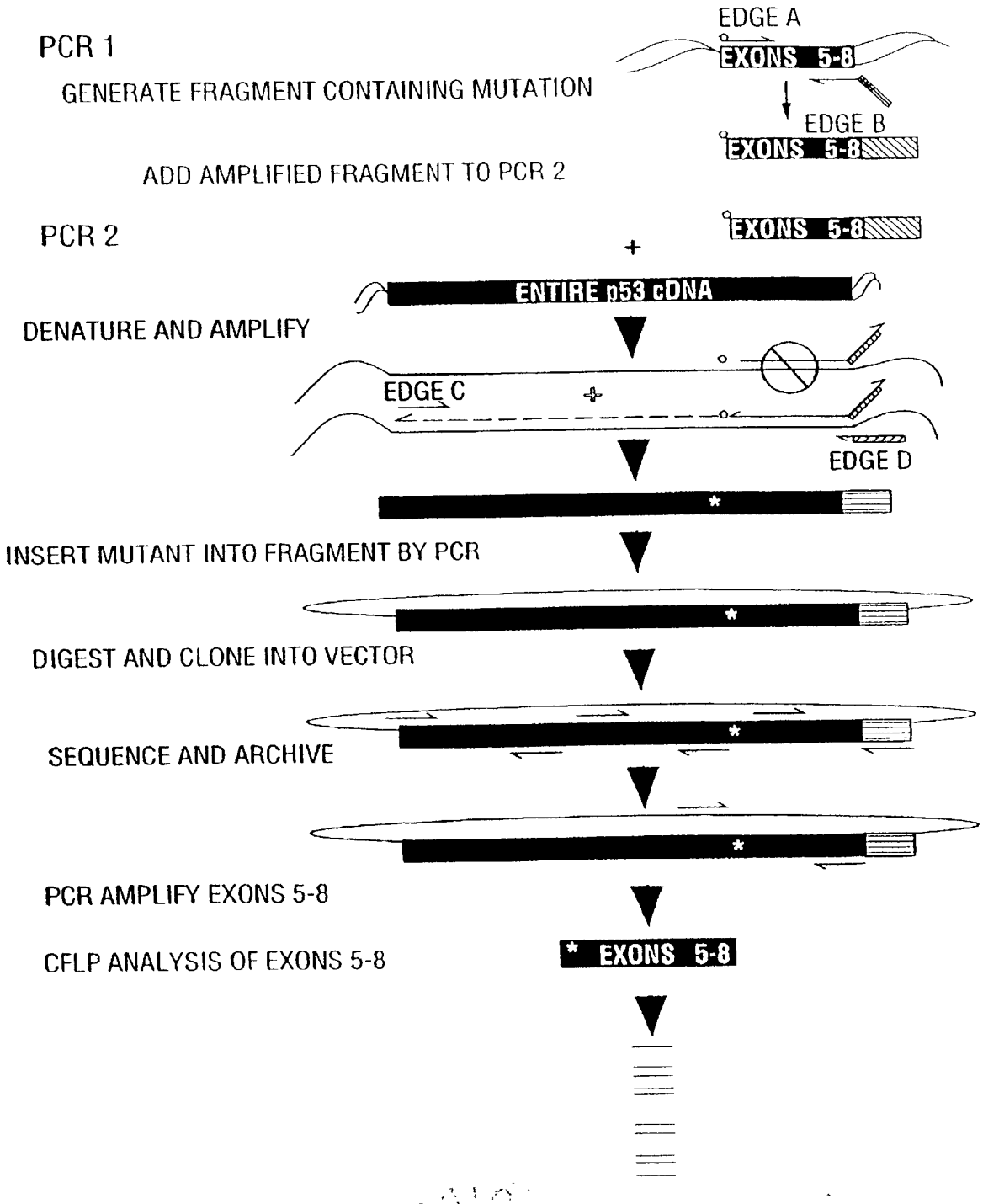

PCR 1
GENERATE FRAGMENT CONTAINING MUTATION
EDGE A
EXONS 5-8
EDGE B
EXONS 5-8
ADD AMPLIFIED FRAGMENT TO PCR 2
PCR 2
EXONS 5-8
+
ENTIRE p53 cDNA
DENATURE AND AMPLIFY
EDGE C
EDGE D
INSERT MUTANT INTO FRAGMENT BY PCR
DIGEST AND CLONE INTO VECTOR
SEQUENCE AND ARCHIVE
PCR AMPLIFY EXONS 5-8
CFLP ANALYSIS OF EXONS 5-8
* EXONS 5-8

FIG. 77

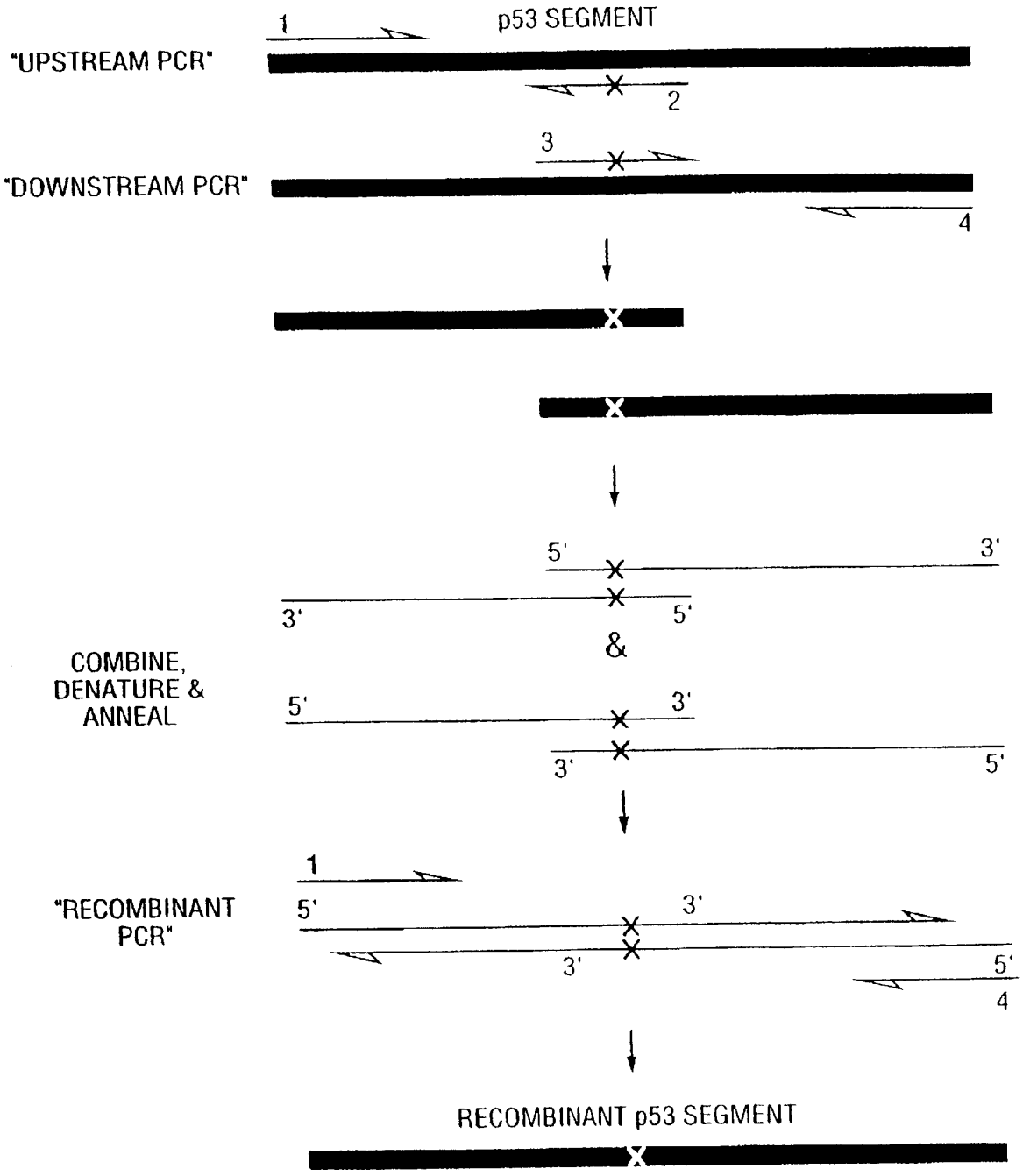

1
p53 SEGMENT
"UPSTREAM PCR"
2
3
"DOWNSTREAM PCR"
4
5'
3'
3'
5'
&
COMBINE, DENATURE & ANNEAL
5'
3'
3'
5'
1
"RECOMBINANT PCR"
5'
3'
3'
5'
4
RECOMBINANT p53 SEGMENT

FIG. 78

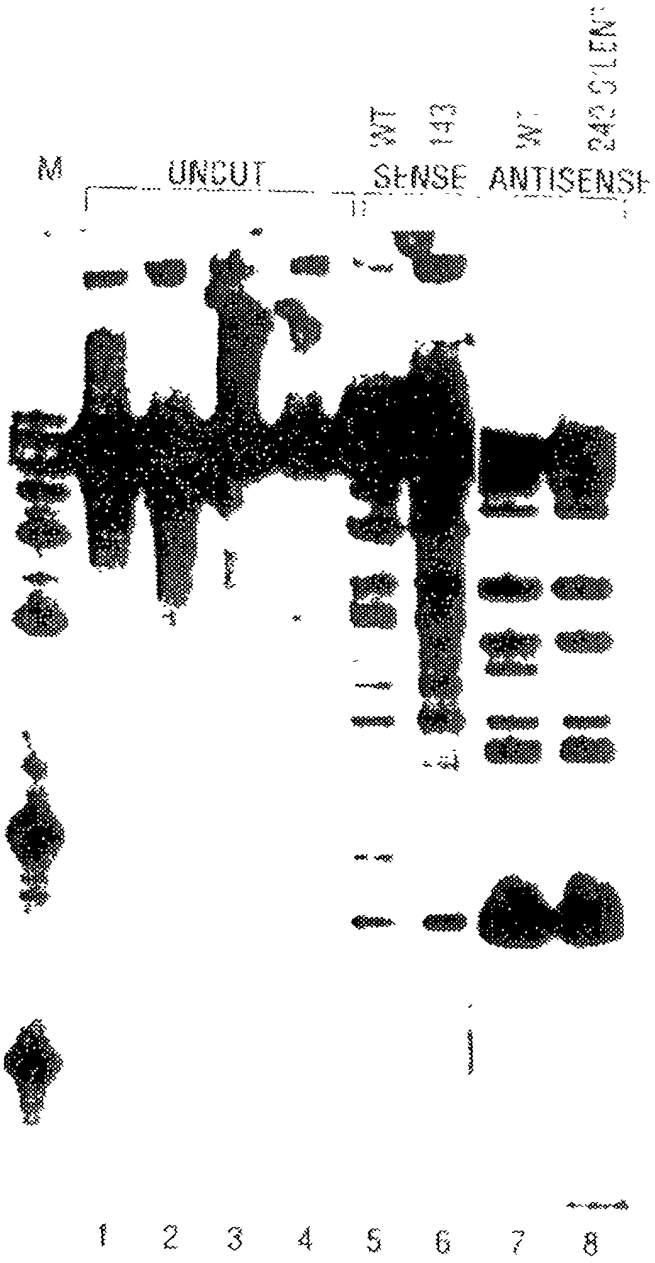


FIG. 79

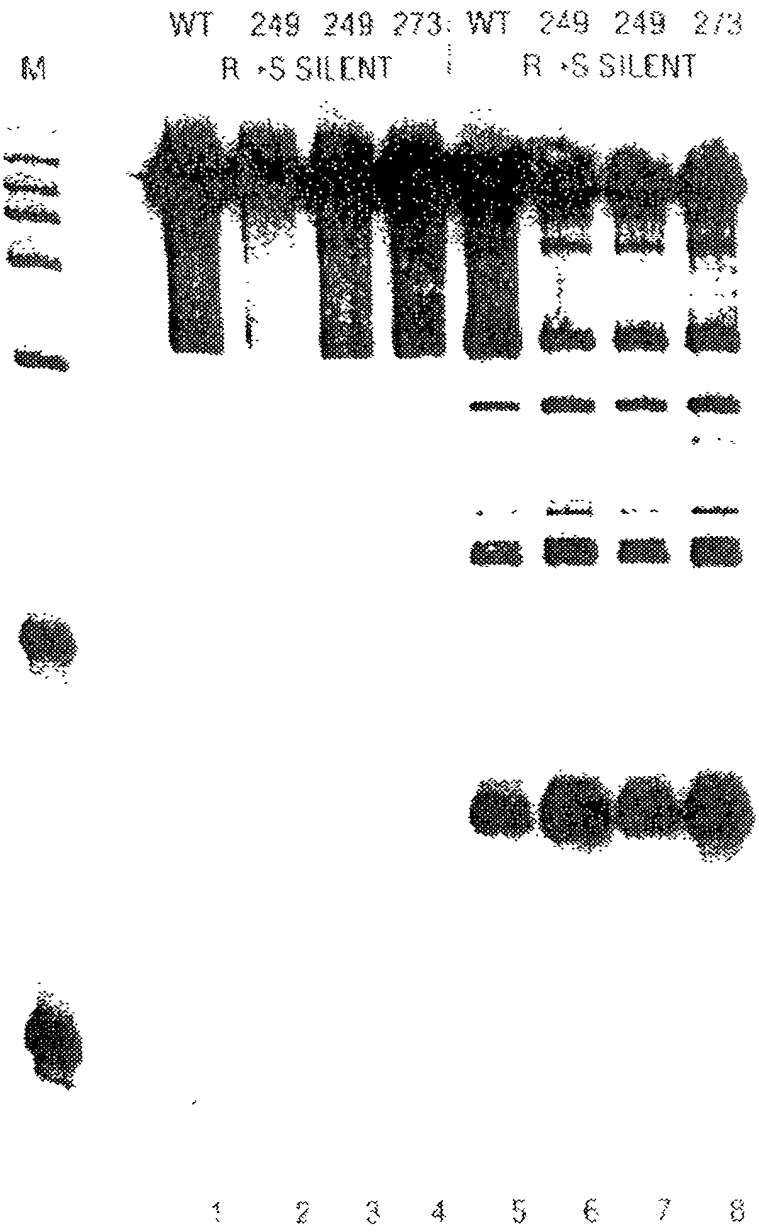


FIG. 80

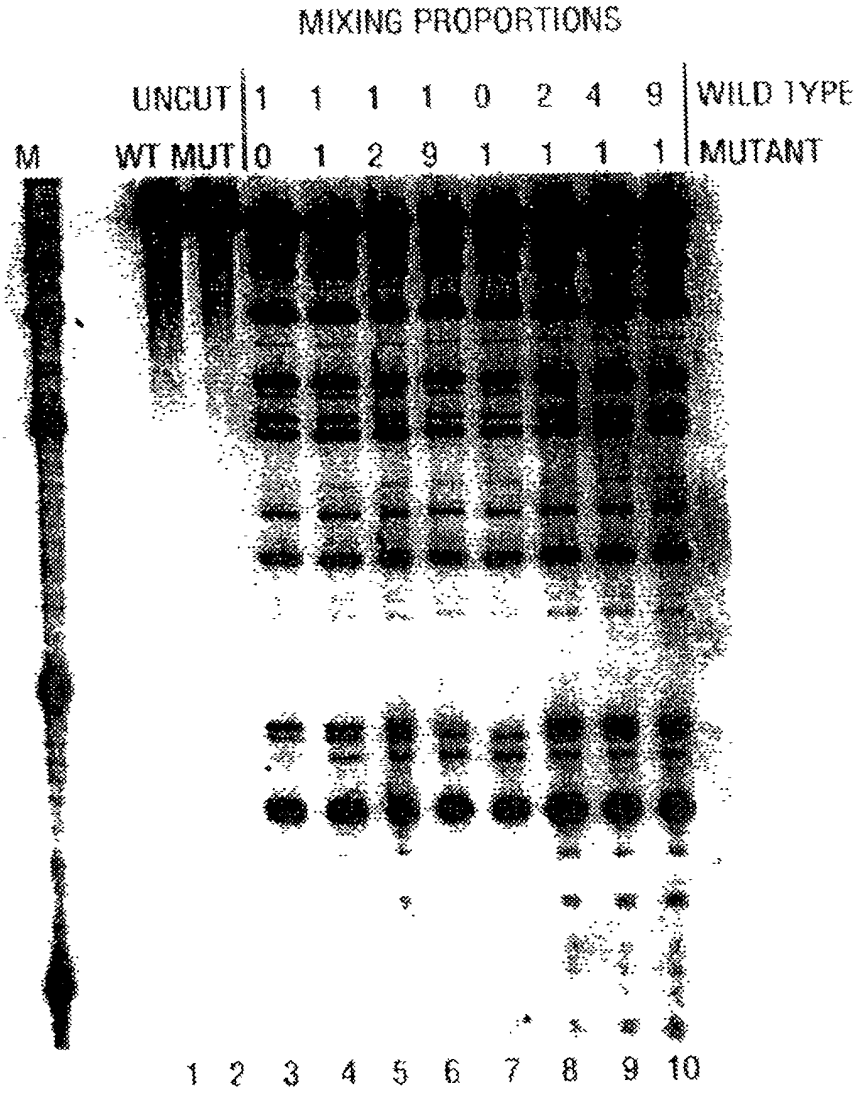

MIXING PROPORTIONS
UNCUT
WT MUT
1 1 1 1 0 2 4 9
0 1 2 9 1 1 1 1
WILD TYPE
MUTANT
M
1 2 3 4 5 6 7 8 9 10

FIG. 81

```
HCV1.1 (SEQ ID NO:121)    1 CTGTCTTCAC GCAGAAAGCG TCTGGCCATG GCGTTAGTAT GAGTGTCGTG 50
HCV2.1 (SEQ ID NO:122)      CTGTCTTCAC GCAGAAAGCG TCTAGCCATG GCGTTAGTAT GAGTGTCGTG
HCV3.1 (SEQ ID NO:123)      CTGTCTTCAC GCAGAAAGCG TCTAGCCATG GCGTTAGTAT GAGTGTCGTG
HCV4.2 (SEQ ID NO:124)      CTGTCTTCAC GCAGAAAGCG TCTAGCCATG GCGTTAGTAT GAGTGTCGTG
HCV6.1 (SEQ ID NO:125)      CTGTCTTCAC GCAGAAAGCG TCTAGCCATG GCGTTAGTAT GAGTGTCGTA
HCV7.1 (SEQ ID NO:126)      CTGTCTTCAC GCAGAAAGCG CCTAGCCATG GCGTTAGTAC GAGTGTCGTG

                           51 CAGCCTCCAG GACCCCCCCT CCCGGGAGAG CCATAGTGGT CTGCGGAACC 100
HCV1.1                        CAGCCTCCAG GACCCCCCCT CCCGGGAGAG CCATAGTGGT CTGCGGAACC
HCV2.1                        CAGCCTCCAG GICCCCCCCT CCCGGGAGAG CCATAGTGGT CTGCGGAACC
HCV3.1                        CAGCCTCCAG GACCCCCCCT CCCGGGAGAG CCATAGTGGT CTGCGGAACC
HCV4.2                        CAGCCTCCAG GCCCCCCCCT CCCGGGAGAG CCATAGTGGT CTGCGGAACC
HCV6.1                        CAGCCTCCAG GACCCCCCCT CCCGGGAGAG CCATAGTGGT CTGCGGAACC
HCV7.1

                          101 GGTGAGTACA CCGGAATTGC CAGGACGACC GGGTCCTTTC TTGGAT-AAA 150
HCV1.1                        GGTGAGTACA CCGGAATTGC CAGGACGACC GGGTCCTTTC TTGGAT-CAA
HCV2.1                        GGTGAGTACA CCGGAATTGC CAGGACGACC GGGTCCTTTC TTGGAT-CAA
HCV3.1                        GGTGAGTACA CCGGAATTGC CAGGACGACC GGGTCCTTTC GTGGATGTAA
HCV4.2                        GGTGAGTACA CCGGAATTGC CGGGAAGACT GGGTCCTTTC TTGGAT-AAA
HCV6.1                        GGTGAGTACA CCGGAATCGC TGGGGTGACC GGGTCCTTTC TTGGAG-CAA
HCV7.1
```

FIG. 82A

```
HCV1.1    151 CCCGCTCAAT GCCTGGAGAT TTGGGCGTGC CCCCGCAAGA CTGCTAGCCG 200
HCV2.1        CCCGCTCAAT GCCTGGAGAT TTGGGCGTGC CCCCGCAAGA CTGCTAGCCG
HCV3.1        CCCGCTCAAT GCCTGGAGAT TTGGGCGTGC CCCCGCGAGA CTGCTAGCCG
HCV4.2        CCCGCTCAAT GCCTGGAGAT TTGGGCGTGC CCCCGCAAGA CTGCTAGCCG
HCV6.1        CCCACTCTAT GCCCGGCCAT TTGGGCGTGC CCCCGCAAGA CTGCTAGCCG
HCV7.1        CCCGCTCAAT ACCCAGAAAT TTGGGCGTGC CCCCGCGAGA TCACTAGCCG

HCVI.1    201 AGTAGTGTTG GGTCGCGAAA GGCCTTGTGG TACTGCCTGA TAGGGTGCCT 250
HCV2.1        AGTAGTGTTG GGTCGCGAAA GGCCTTGTGG TACTGCCTGA TAGGGTGCTT
HCV3.1        AGTAGTGTTG GGTCGCGAAA GGCCTTGTGG TACTGCCTGA TAGGGTGCTT
HCV4.2        AGTAGTGTTG GGTCGCGAAA GGCCTTGTGG TACTGCCTGA TAGGGTGCTT
HCV6.1        AGTAGCGTTG GGTTGCGAAA GGCCTTGTGG TACTGCCTGA TAGGGTGCTT
HCV7.1        AGTAGTGTTG GGTCGCGAAA GGCCTTGTGG TACTGCCTGA TAGGGTGCTT

HCVI.1    251 GCGAGTGCCC CGGGAGGTCT CGTAGACCGT GC 282
HCV2.1        GCGAGTGCCC CGGGAGGTCT CGTAGACCGT GC
HCV3.1        GCGAGTGCCC CGGGAGGTCT CGTAGACCGT GC
HCV4.2        GCGAGTGCCC CGGGAGGTCT CGTAGACCGT GC
HCV6.1        GCGAGTACCC CGGGAGGTCT CGTAGACCGT GC
HCV7.1        GCGAGTGCCC CGGGAGGTCT CGTAGACCGT GC
```

FIG. 82B

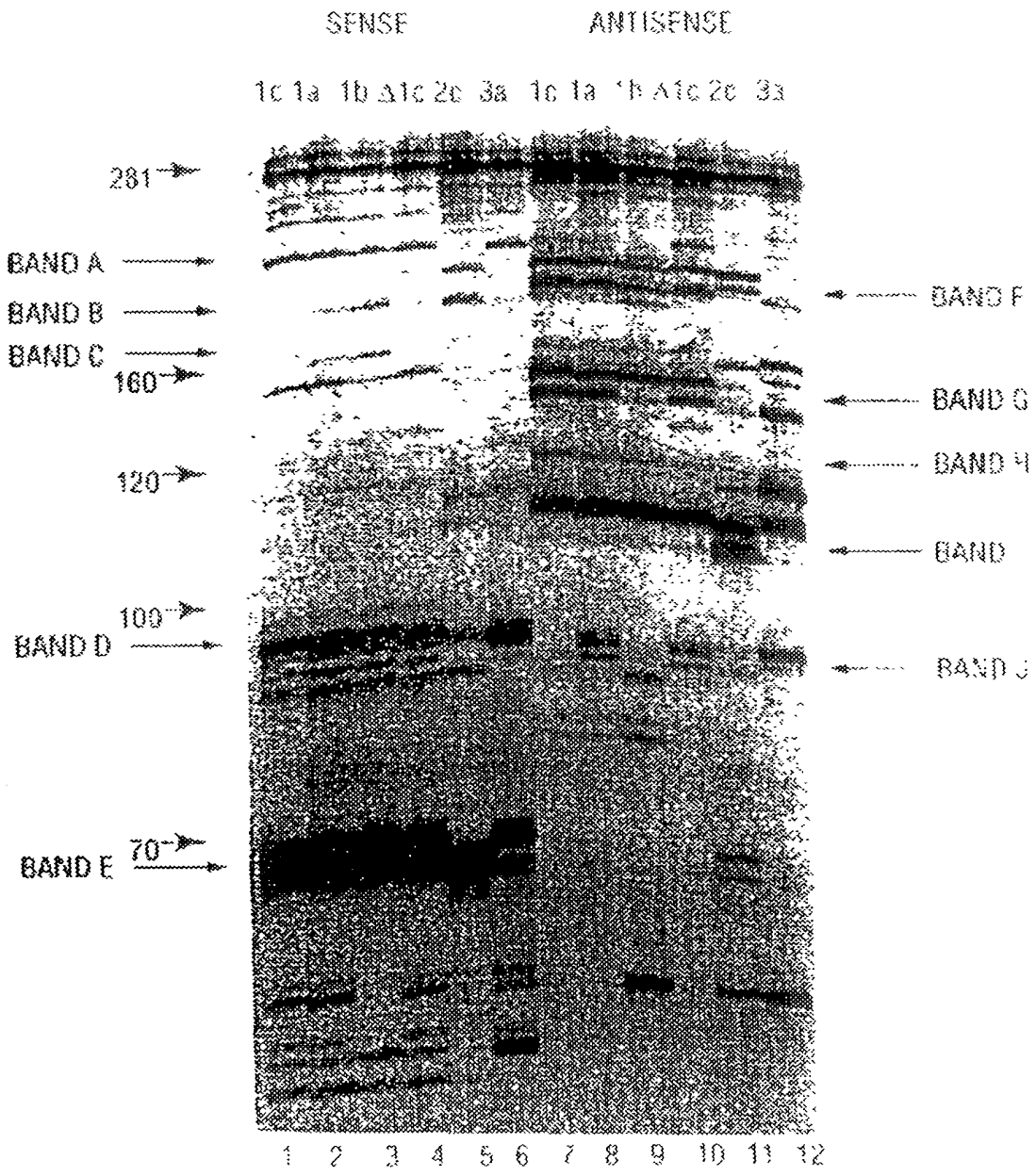

SENSE
ANTISENSE
1c 1a 1b Δ1c 2c 3a 1c 1a 1b Δ1c 2c 3a
281
BAND A
BAND B
BAND C
160
120
100
BAND D
70
BAND E
BAND F
BAND G
BAND H
BAND
BAND J
1 2 3 4 5 6 7 8 9 10 11 12

FIG. 83

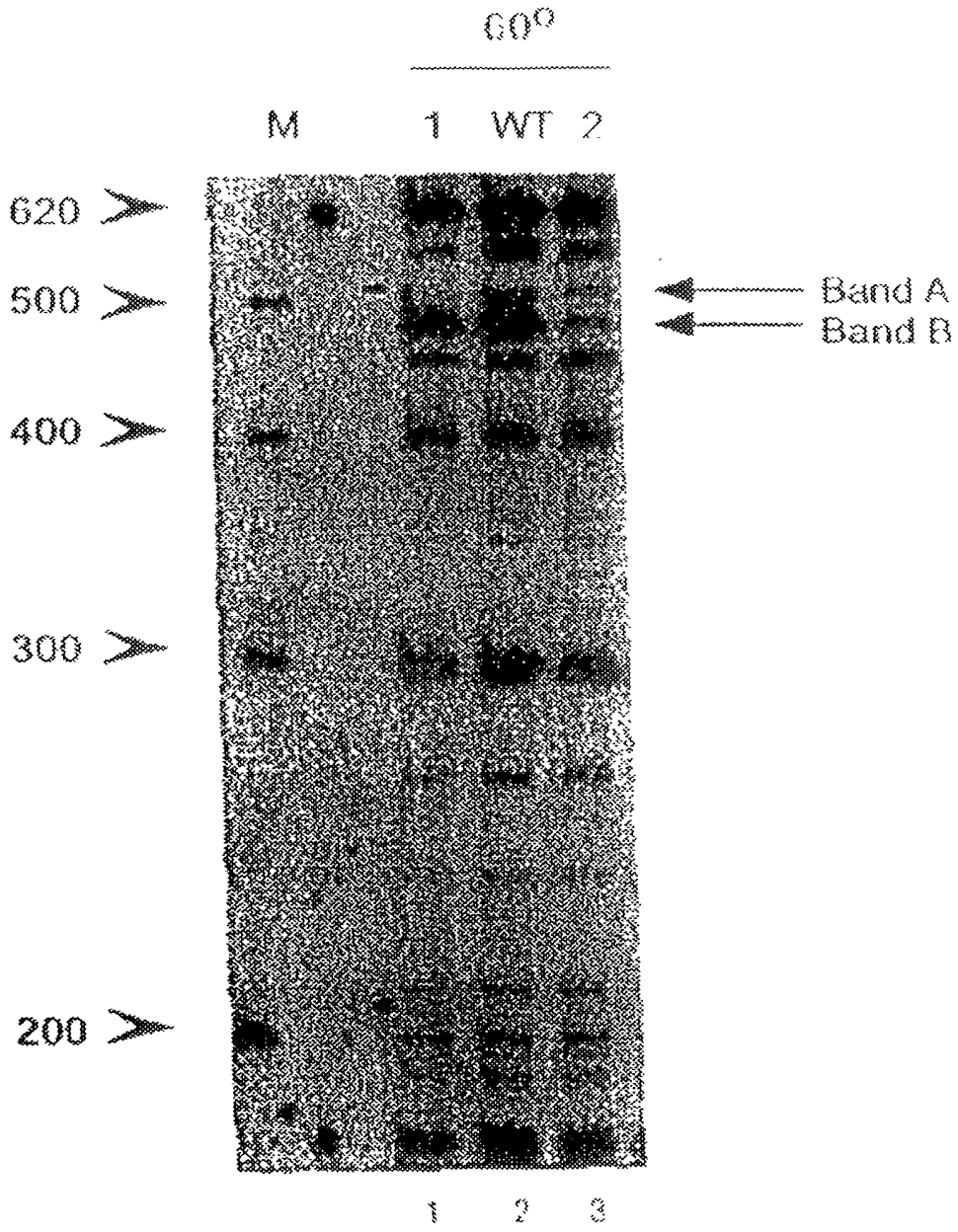


FIG. 84

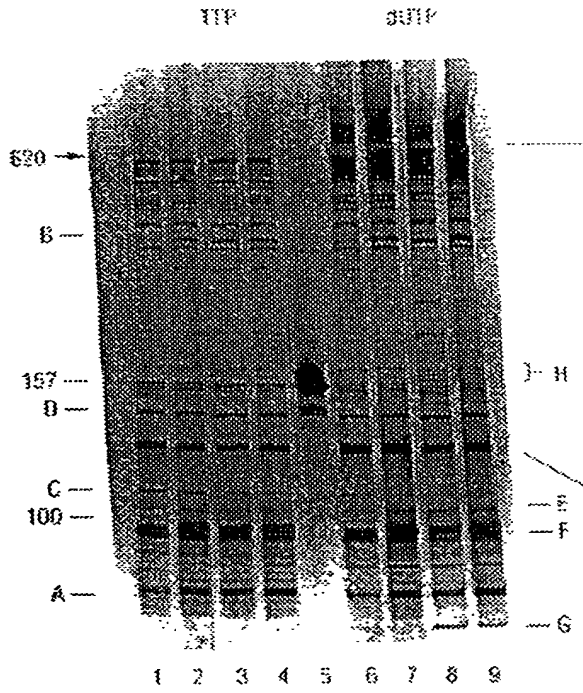


FIG. 85A

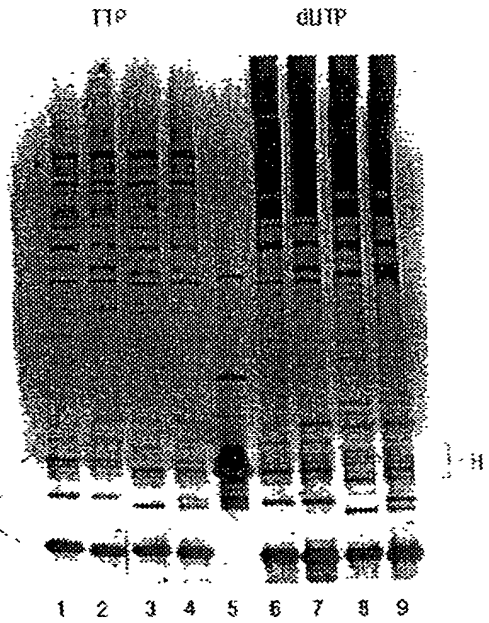


FIG. 85B

SENSE STRAND

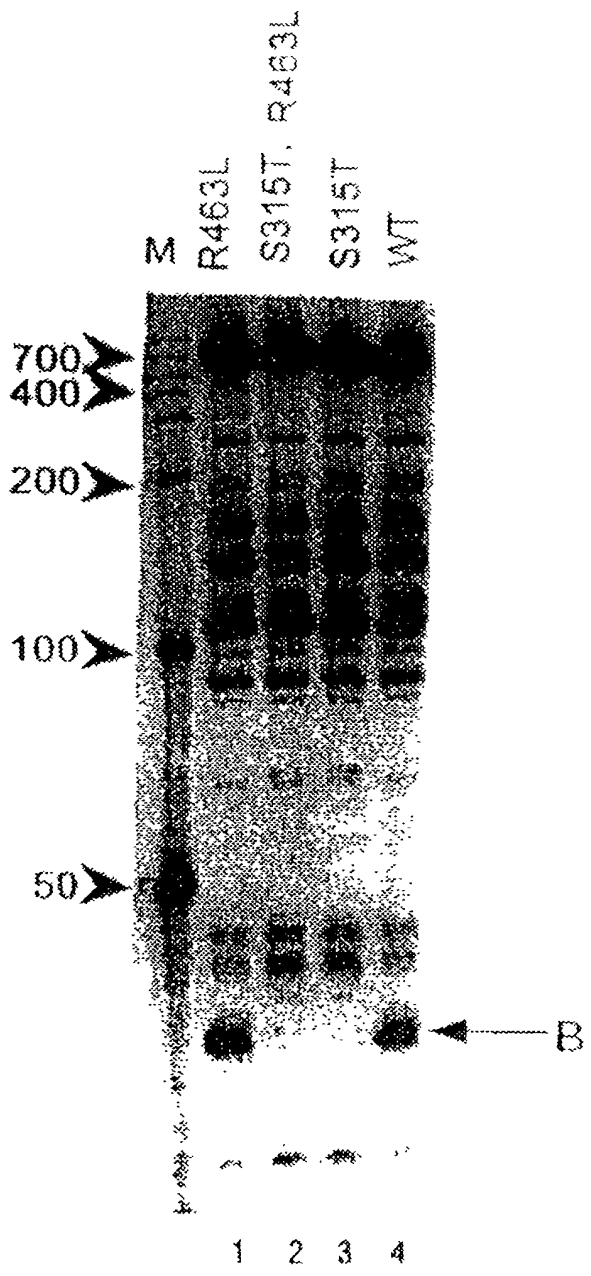


FIG. 86

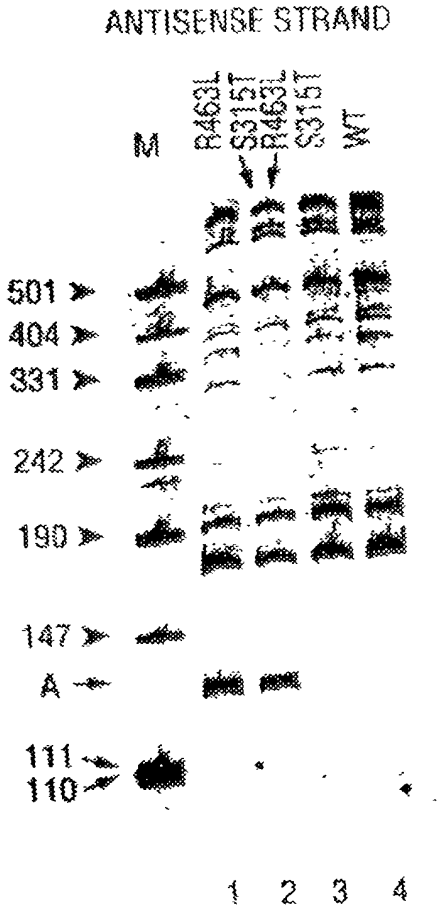

ANTISENSE STRAND
M
R463L
S315T
R463L
S315T
WT
501
404
331
242
190
147
A
111
110
1
2
3
4

FIG. 87

```
        10          20          30          40          50          60
       AGA GTTTGATCCT GGCTCAG                                          1638
AAATTGAAGA GTTTGATCAT GGCTCAGATT GAACGCTGGC GGCAGGCCTA ACACATGCAA
TTTAACTTCT CAAACTAGTA CCGAGTCTAA CTTGCGACCG CCGTCCGGAT TGTGTACGTT

        70          80          90         100         110         120
                                                GGCGGAC GGGTGAGTAA  ER10
GTCGAACGGT AACAGGAAGA AGCTTGCTTC TTTGCTGACG AGTGGCGGAC GGGTGAGTAA
CAGCTTGCCA TTGTCCTTCT TCGAACGAAG AAACGACTGC TCACCGCCTG CCCACTCATT

       130         140         150         160         170         180
TGTCTGGGAA ACTGCCTGAT GGAGGGGGAT AACTACTGGA AACGGTAGCT AATACCGCAT
ACAGACCCTT TGACGGACTA CCTCCCCCTA TTGATGACCT TTGCCATCGA TTATGGCGTA

       190         200         210         220         230         240
AACGTCGCAA GACCAAAGAG GGGGACCTTC GGGCCTCTTG CCATCGGATG TGCCCAGATG
TTGCAGCGTT CTGGTTTCTC CCCCTGGAAG CCCGGAGAAC GGTAGCCTAC ACGGGTCTAC

       250         260         270         280         290         300
GGATTAGCTA GTAGGTGGGG TAACGGCTCA CCTAGGCGAC GATCCCTAGC TGGTCTGAGA
CCTAATCGAT CATCCACCCC ATTGCCGAGT GGATCCGCTG CTAGGGATCG ACCAGACTCT

       310         320         330         340         350         360
GGATGACCAG CCACACTGGA ACTGAGACAC GGTCCAGACT CCTACGGGAG GCAGCAGTGG
CCTACTGGTC GGTGTGACCT TGACTCTGTG CCAGGTCTGA GGATGCCCTC CGTCGTCACC
                                    TGA GGATGCCCTC CGTCGTC           1659
```

FIG. 88A

```
        370         380         390         400         410         420
GGAATATTGC ACAATGGGCG CAAGCCTGAT GCAGCCATGC CGCGTGTATG AAGAAGGCCT
CCTTATAACG TGTTACCCGC GTTCGGACTA CGTCGGTACG GCGCACATAC TTCTTCCGGA

        430         440         450         460         470         480
TCGGGTTGTA AAGTACTTTC AGCGGGGAGG AAGGGAGTAA AGTTAATACC TTTGCTCATT
AGCCCAACAT TTCATGAAAG TCGCCCCTCC TTCCCTCATT TCAATTATGG AAACGAGTAA

        490         500         510         520         530         540
GACGTTACCC GCAGAAGAAG CACCGGCTAA CTCCGTGCCA GCAGCCGCGG TAATACGGAG
CTGCAATGGG CGTCTTCTTC GTGGCCGATT GAGGCACGGT CGTCGGCGCC ATTATGCCTC

        550         560         570         580         590         600
GGTGCAAGCG TTAATCGGAA TTACTGGGCG TAAAGCGCAC GCAGGCGGTT TGTTAAGTCA
CCACGTTCGC AATTAGCCTT AATGACCCGC ATTTCGCGTG CGTCCGCCAA ACAATTCAGT

        610         620         630         640         650         660
GATGTGAAAT CCCCGGGCTC AACCTGGGAA CTGCATCTGA TACTGGCAAG CTTGAGTCTC
CTACACTTTA GGGGCCCGAG TTGGACCCTT GACGTAGACT ATGACCGTTC GAACTCAGAG

        670         680         690         700         710         720
GTAGAGGGGG GTAGAATTCC AGGTGTAGCG GTGAAATGCG TAGAGATCTC GAGGAATACC
CATCTCCCCC CATCTTAAGG TCCACATCGC CACTTTACGC ATCTCTAGAC CTCCTTATGG

        730         740         750         760         770         780
GGTGGCGAAG GCGGCCCCCT GGACGAAGAC TGACGCTCAG GTGCGAAAGC GTGGGGAGCA
CCACCGCTTC CGCCGGGGGA CCTGCTTCTG ACTGCGAGTC CACGCTTTCG CACCCCTCGT
```

FIG. 88B

```
       790        800        810        820        830        840
AACAGGATTA GATACCCTGG TAGTCCACGC CGTAAACGAT GTCGACTTGG AGGTTGTGCC
TTGTCCTAAT CTATGGGACC ATCAGGTGCG GCATTTGCTA CAGCTGAACC TCCAACACGG

       850        860        870        880        890        900
CTTGAGGCGT GGCTTCCGGA GCTAACGCGT TAAGTCGACC GCCTGGGGAG TACGGCCGCA
GAACTCCGCA CCGAAGGCCT CGATTGCGCA ATTCAGCTGG CGGACCCCTC ATGCCGGCGT

       910        920        930        940        950        960
AGGTTAAAAC TCAAATGAAT TGACGGGGGC CCGCACAAGC GGTGGAGCAT GTGGTTTAAT
TCCAATTTTG AGTTTACTTA ACTGCCCCCG GGCGTGTTCG CCACCTCGTA CACCAAATTA

       970        980        990       1000       1010       1020
TCGATGCAAC GCGAAGAACC TTACCTGGTC TTGACATCCA CGGAAGTTTT CAGAGATGAG
AGCTACGTTG CGCTTCTTGG AATGGACCAG AACTGTAGGT GCCTTCAAAA GTCTCTACTC

      1030       1040       1050       1060       1070       1080
AATGTGCCTT CGGGAACCGT GAGACAGGTG CTGCATGGCT GTCGTCAGCT CGTGTTGTGA
TTACACGGAA GCCCTTGGCA CTCTGTCCAC GACGTACCGA CAGCAGTCGA GCACAACACT

      1090       1100       1110       1120       1130       1140
                   GC AACGAGCGCA ACCC                                  SB-1

AATGTTGGGT TAAGTCCCGC AACGAGCGCA ACCCTTATCC TTTGTTGCCA GCGGTCCGGC
TTACAACCCA ATTCAGGGCG TTGCTCGCGT TGGGAATAGG AAACAACGGT CGCCAGGCCG

      1150       1160       1170       1180       1190       1200
                                                   ATG ACGTCAAGTC      SB-3
                                                   ATG ACGTCAAGTC      SB-4

CGGGAACTCA AAGGAGACTG CCAGTGATAA ACTGGAGGAA GGTGGGGATG ACGTCAAGTC
GCCCTTGAGT TTCCTCTGAC GGTCACTATT TGACCTCCTT CCACCCCTAC TGCAGTTCAG
```

FIG. 88C

```
       1210       1220       1230       1240       1250       1260
ATCATGGCCC TTA                                                          SB-3
ATCATGGCCC TTACGA                                                       SB-4
ATCATGGCCC TTACGACCAG GGCTACACAC GTGCTACAAT GGCGCATACA AAGAGAAGCG
TAGTACCGGG AATGCTGGTC CCGATGTGTG CACGATGTTA CCGCGTATGT TTCTCTTCGC

       1270       1280       1290       1300       1310       1320
ACCTCGCGAG AGCAAGCGGA CCTCATAAAG TGCGTCGTAG TCCGGATTGG AGTCTGCAAC
TGGAGCGCTC TCGTTCGCCT GGAGTATTTC ACGCAGCATC AGGCCTAACC TCAGACGTTG

       1330       1340       1350       1360       1370       1380
TCGACTCCAT GAAGTCGGAA TCGCTAGTAA TCGTGGATCA GAATGCCACG GTGAATACGT
AGCTGAGGTA CTTCAGCCTT AGCGATCATT AGCACCTAGT CTTACGGTGC CACTTATGCA
                                                    GC CACTTATGCA   1743

       1390       1400       1410       1420       1430       1440
TCCCGGGCCT TGTACACACC GCCCGTCACA CCATGGGAGT GGGTTGCAAA AGAAGTAGGT
AGGGCCCGGA ACATGTGTGG CGGGCAGTGT GGTACCCTCA CCCAACGTTT TCTTCATCCA   1743
AGGGCCCGGA ACATG

       1450       1460       1470       1480       1490       1500
AGCTTAACCT TCGGGAGGGC GCTTACCACT TTGTGATTCA TGACTGGGGT GAAGTCGTAA
TCGAATTGGA AGCCCTCCCG CGAATGGTGA AACACTAAGT ACTGACCCCA CTTCAGCATT

       1510       1520       1530       1540       1550
CAAGGTAACC GTAGGGGAAC CTGCGGTTGG ATCACCTCCT TA........
GTTCCATTGG CATCCCCTTG GACGCCAACC TAGTGGAGGA AT........
```

FIG. 88D

```
                                          AGAGTTTGATCCTGGCTCAG
1638 (SEQ ID NO:151)
E.colirrsE(SEQ ID NO:158)0 ...AAATTGAAGAGTTTGATCATGGCTCAGATTGAACGCTGGCGGCAGGCCTAACACATGCA
Cam.jejun5(SEQ ID NO:159)0 ~TTTTTATGGAGAGTTTGATCCTGGCTCAGAGTGAACGCTGGCGGCGTGCCTAATACATGCA
Stp.aureus(SEQ ID NO:160)0 ..TTTTATGGAGAGTTTGATCCTGGCTCAGGATGAACGCTGGCGGCGTGCCTAATACATGCA

                                                                             GGCGGACGGG
ER10 (SEQ ID NO:152)
E.colirrsE                 60 AGTCGAACGGTAACAG----GAAGAAGCTTGCTTCTTT----GCTGACGAGTGGCGGACGGG
Cam.jejunS                 62 AGTCGAACGAT-----GAAGCTTCTAGCTTGCTAGAAGTGGA-----TTAGTGGCGCACGGG
Stp.aureus                 61 AGTCGAGCGAA-----CGGACGAGAAGCTTGCTTCTCTGATG----TT-AGCGGCGGACGGG

                              TGAGTAA
ER10
E.colirrsE                114 TGAGTAATGTCTGGGA-AACTGCCTGATGGAGGGGGATAACTACTGGAAACGGTAGCTAATA
Cam.jejun5                114 TGAGTAAGGTATAGTTAATCTGCCCTACACAAGAGGACAACAGTTGGAAACGACTGCTAATA
Stp.aureus                113 TGAGTAACACGTGGATAACCTACCTATAAGACTGGGATAACTTCGGGAAACCGGAGCTAATA

E.colirrsE                175 CCGCATAAC-------GTCGCAAGAC--------CAAAGAGGGGGACCTTCG-GGCCTCTTG
Cam.jejun5                176 CTCTATACTCCTGCTTAACACAAGTTGAGTAGG-GAAAG---------TTTTT-------CG
Stp.aureus                175 CCGGATAATATTTTGAACCGCATGGTTCAAAAGTGAAAGACGGT----CTT----GCTGTCA

E.colirrsE                221 CCATCGGATGTGCCCAGATGGGATTAGCTAGTAGGTGGGGTAACGGCTCACCTAGGCGACGA
Cam.jejun5                221 GTGTAGGATGAGACTATATAGTATCAGCTAGTTGGTAAGGTAATGGCTTACCAAGGCTATGA
Stp.aureus                229 CTTATAGATGGATCCGCGCTGCATTAGCTAGTTGGTAAGGTAACGGCTTACCAAGGCAACGA

E.colirrsE                283 TCCCTAGCTGGTCTGAGAGGATGACCAGCCACACTGGAACTGAGACACGGTCCAGACTCCTA
Cam.jejun5                283 CGCTTAACTGGTCTGAGAGGATGATCAGTCACACTGGAACTGAGACACGGTCCAGACTCCTA
Stp.aureus                291 TACGTAGCCGACCTGAGAGGGTGATCGGCCACACTGGAACTGAGACACGGTCCAGACTCCTA
1659(COMPL)                                                                       ACTCCTA
```

FIG. 89A

```
                345 CGGGAGGCAGCAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCCATGCCGCGTG
E.colirrsE      345 CGGGAGGCAGCAGTAGGGAATATTGCGCAATGGGGGAAACCCTGACGCAGCAACGCCGCGTG
Cam.jejun5      353 CGGGAGGCAGCAGTAGGGAATCTTCCGCAATGGGCGAAAGCCTGACGGAGCAACGCCGCGTG
Stp.aureus          CGGGAGGCAGCAG
1659(COMPL)

                407 TATGAAGAAGGCCTTCGGGTTGTAAAGTACTTTCAGCGGGGAGGAA-GGGAGTAAAGTTAAT
E.colirrsE      407 GAGGATGACACTTTTCGGAGCGTAAACTCCTTTTCTTAGGGAAG ------------AATT
Cam.jejun5      415 AGTGATGAAGGTCTTCGGATCGTAAAACTCTGTTATTAGGGAAGAACATATGTGTAAGTAAC
Stp.aureus

                468 ACCTTTGCTCATTGACGTTACCCGCAGAAGAAGCACCGGCTAACTCCGTGCCAGCAGCCGCG
E.colirrsE      455 C----------TGACGGTACCTAAGGAATAAGCACCGGCTAACTCCGTGCCAGCAGCCGCG
Cam.jejun5      476 -TGTGCACATCTTGACGGTACCTAATCAGAAAGCCACGGCTAACTACGTGCCAGCAGCCGCG
Stp.aureus
```

FIG. 89B

```
E.colirrsE   530 GTAATACGGAGGGTGCAAGCGTTAATCGGAATTACTGGGCGTAAAGCGCACGCAGGCGGTTT
Cam.jejun5   506 GTAATACGGAGGGTGCAAGCGTTACTCGGAATCACTGGGCGTAAAGGGCGCGTAGGCGGATT
Stp.aureus   538 GTAATACGTAGGTGGCAAGCGTTATCCGGAATTATTGGGCGTAAAGCGCGCGTAGGCGGTTT

E.colirrsE   592 GTTAAGTCAGATGTGAAATCCCCGGGCTCAACCTGGGAACTGCATCTGATACTGGCAAGCTT
Cam.jejun5   568 ATCAAGTCTCTTGTGAAATCTAATGGCTTAACCATTAAACTGCTTGGGAAACTGATAGTCTA
Stp.aureus   600 TTTAAGTCTGATGTGAAAGCCCACGGCTCAACCGTGGAGGGTCATTGGAAACTGGAAAACTT

E.colirrsE   654 GAGTCTCGTAGAGGGGGGTAGAATTCCAGGTGTAGCGGTGAAATGCGTAGAGATCTGGAGGA
Cam.jejun5   630 GAGTGAGGGAGAGGCAGATGGAATTGGTGGTGTAGGGGTAAAATCCGTAGATATCACCAAGA
Stp-aureus   662 GAGTGCAGAAGAGGAAAGTGGAATTCCATGTGTAGCGGTGAAATGCGCAGAGATATGGAGGA

E.colirrsE   716 ATACCGGTGGCGAAGGCGGCCCCCTGGACGAAGACTGACGCTCAGGTGCGAAAGCGTGGGGA
Cam.jejun5   692 ATACCCATTGCGAAGGCGATCTGCTGGAACTCAACTGACGCTAAGGCGCGAAAGCGTGGGGA
Stp.aureus   724 ACACCAGTGGCGAAGGCGACTTTCTGGTCTGTAACTGACGCTGATGTGCGAAAGCGTGGGGA

E.colirrsE   778 GCAAACAGGATTAGATACCCTGGTAGTCCACGCCGTAAACGATGTCGACTTGGAGGTTGTGC
Cam.jejun5   754 GCAAACAGGATTAGATACCCTGGTAGTCCACGCCCTAAACGATGTACACTAGTTGTTGGGGT
Stp.aureus   786 TCAAACAGGATTAGATACCCTGGTAGTCCACGCCGTAAACGATGAGTGCTAAGTGTTAGGGG
```

FIG. 89C

```
E.colirrsE   840  C-CTTGA-GGCGTGGCTTCCGGAGCTAACGCGTTAAGTCGACCGCCTGGGGAGTACGGCCGC
Cam.jejun5   816  G-CTAGT-CATCTCAGTAATGCAGCTAACGCATTAAGTGTACCGCCTGGGGAGTACGGTCGC
Stp.aureus   848  GT-TTCCGCCCCTTAGTGCTGCAGCTAACGCATTAAGCACTCCGCCTGGGGAGTACGACCGC

E.colirrsE   900  AAGGTTAAAACTCAAATGAATTGACGGGGGCCCGCACAAGCGGTGGAGCATGTGGTTTAATT
Cam.jejun5   876  AAGATTAAAACTCAAAGGAATAGACGGGGACCCGCACAAGCGGTGGAGCATGTGGTTTAATT
Stp.aureus   909  AAGGTTGAAACTCAAAGGAATTGACGGGGACCCGCACAAGCGGTGGAGCATGTGGTTTAATT

E.colirrsE   962  CGATGCAACGCGAAGAACCTTACCTGGTCTTGACATCCACGGAAGTTTTCAGAGATGAGAAT
Cam.jejun5   938  CGAAGATACGCGAAGAACCTTACCTGGGCTTGATATCCTAAGAACCTTTTAGAGATAAGAGG
Stp.aureus   971  CGAAGCAACGCGAAGAACCTTACCAAATCTTGACATCCTTTGACAACTCTAGAGATAGAGCC

E.colirrsE  1024  GTG--CCTTCGGG--AA-CCGTGAGACAGGTGCTGCATGGCTGTCGTCAGCTCGTGTTGTGA
Cam.jejun5  1000  GTGCTAGCTTGCTAGAA-CTTAGAGACAGGTGCTGCACGGCTGTCGTCAGCTCGTGTCGTGA
Stp.aureus  1033  TTCC-CCTTCGGG--GGACAAAGTGACAGGTGGTGCATGGTTGTCGTCAGCTCGTGTCGTGA

SB-1                                   GCAACGAGCGCAACCC
E.colirrsE  1081  AATGTTGGGTTAAGTCCCGCAACGAGCGCAACCCTTATCCTTTGTTGCCAGCGGTCCGG-CC
Cam.jejun5  1061  GATGTTGGGTTAAGTCCCGCAACGAGCGCAACCCACGTATTTAGTTGCTAACGGTTCGG-CC
Stp.aureus  1092  GATGTTGGGTTAAGTCCCGCAACGAGCGCAACCCTTAAGCTTAGTTGCCATCA-TTAAGT-T
```

FIG. 89D

```
                                                                                                ATGACGTCAAGTCATC
SB-3 (SEQ ID NO:157)                                                                            ATGACGTCAAGTCATC
SB-4 (SEQ ID NO:154)
E.colirrsE  1142 GGGAACTCAAAGGAGACTGCCAGTGATAAACTGGAGGAAGGTGGGGATGACGTCAAGTCATC
Cam.jejun5  1122 GAGCACTCTAAATAGACTGCCTTCG-TAAGGAGGAGGAAGGTGTGGACGACGTCAAGTCATC
Stp.aureus  1152 GGGCACTCTAAGTTGACTGCCGGTGACAAACCGGAGGAAGGTGGGGATGACGTCAAATCATC

SB-3                ATGGCCCTTA
SB-4                ATGGCCCTTACGA
E.colirrsE  1204 ATGGCCCTTACGACCAGGGCTACACACGTGCTACAATGGCGCATACAAAGAGAAGCGACCTC
Cam.jejun5  1183 ATGGCCCTTATGCCCAGGGCGACACACGTGCTACAATGGCATATAGAATGAGACGCAATACC
Stp.aureus  1214 ATGCCCCTTATGATTTGGGCTACACACGTGCTACAATGGACAATACAAAGGGCAGCGAAACC

E.colirrsE  1266 GCGAGAGCAAGCGGACCTCATAAAGTGCGTCGTAGTCCGGATTGGAGTCTGCAACTCGACTC
Cam.jejun5  1245 GCGAGGTGGAG-CAAATCTATAAAATATGTCCCAGTTCGGATTGTTCTCTGCAACTCGAGAG
Stp.aureus  1276 GCGAGGTCAAGCAAATCCCATAAAGTTGTTCTCAGTTCGGATTGTAGTCTGCAACTCGACTA

E.colirrsE  1328 CATGAAGTCGGAATCGCTAGTAATCGTGGATCAGA-ATGCCACGGTGAATACGTTCCCGGGC
Cam.jejun5  1306 CATGAAGCCGGAATCGCTAGTAATCGTAGATCAGCCATGCTACGGTGAATACGTTCCCGGGT
Stp.aureus  1338 CATGAAGCTGGAATCGCTAGTAATCGTAGATCAGC-ATGCTACGGTGAATACGTTCCCGGGT
                                                                                CGGTGAATACGTTCCCGGGC
1743(compl)
```

FIG. 89E

```
E.colirrsE      1389 CTTGTACACACCGCCCGTCACACCATGGGAGTGGGTTGCAAAAGAAGTAGGTAGCTTAACCT
Cam.jejun5      1368 CTTGTACTCACCGCCCGTCACACCATGGGAGTTGATTTCACTCGAAGCCGGAATACT--A-A
Stp.aureus      1399 ATTGTACACACCGCCCGTCACACCACGAGAGTTTGTAACACCCGAAGCCGGTGGAGTAACCT
1743(compl)          CTTGTAC

E.colirrsE      1451 TCG-GGAGGGCGCTTACCACTTTGTGATTCATGACTGGGGTGAAGTCGTAACAAGGTAACCG
Cam.jejun5      1427 AC---T-AGTTACCGTCCACAGTGGAATCAGCGACTGGGGTGAAGTCGTAACAAGGTAACCG
Stp.aureus      1461 TTTAGGAGCTAGCCGTCGAAGGTGGGACAAATGATTGGGGTGAAGTCGTAACAAGGTAGCCG

E.colirrsE      1512 TAGGGGAACCTGCGGTTGGATCACCTCCTTA---
Cam.jejun5      1485 TAGGAGAACCTGCGGTTGGATCACCTCCT-----
Stp.aureus      1523 TATCGGAAGGTGCGGCTGGATCACCTCCTTTCT-
```

FIG. 89F

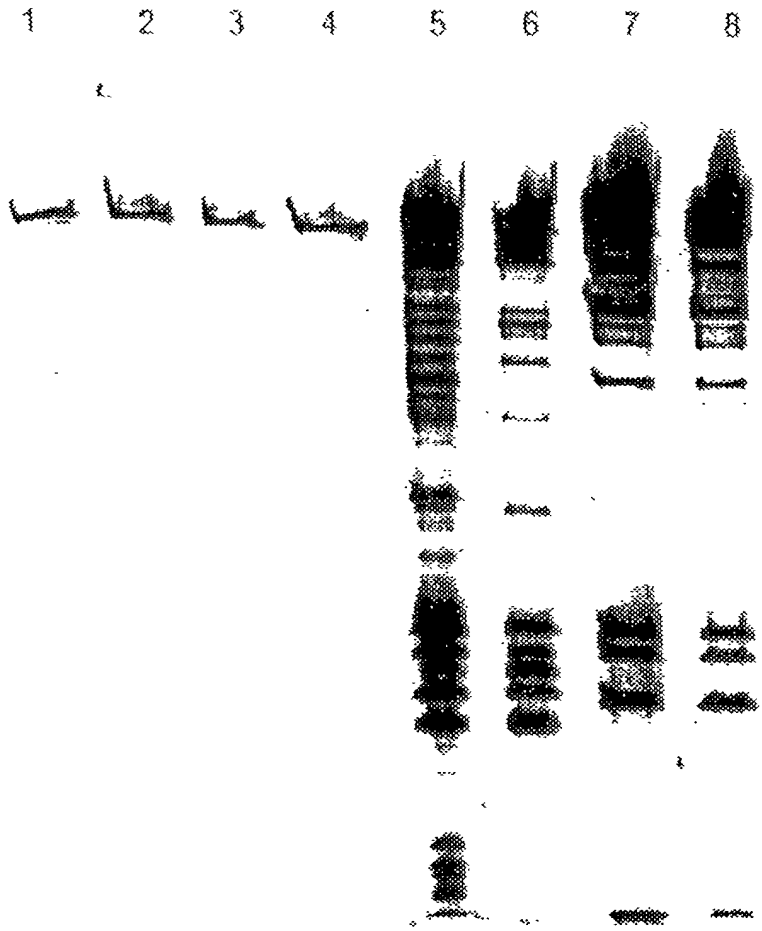


FIG. 90

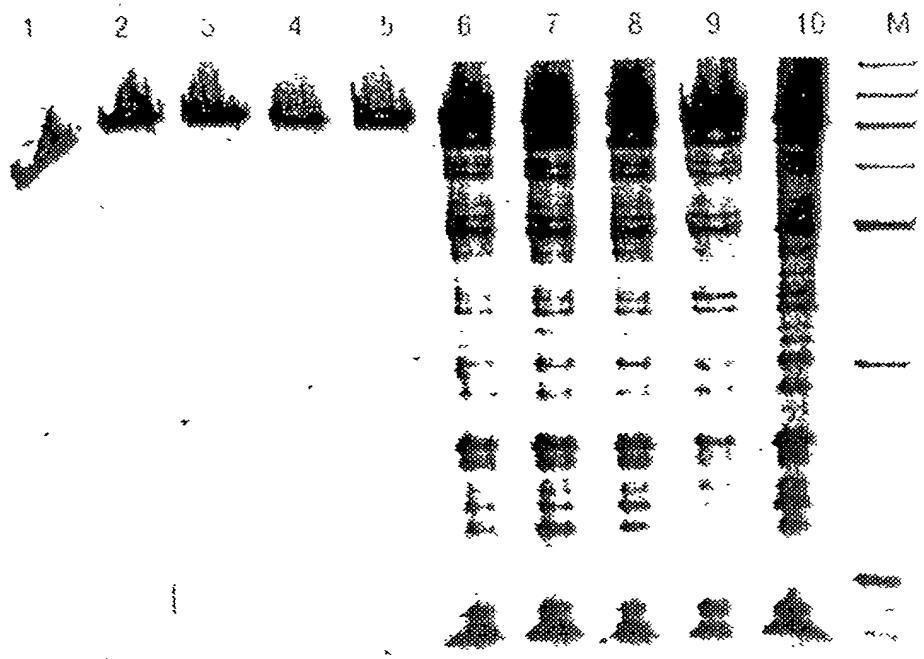


FIG. 91A

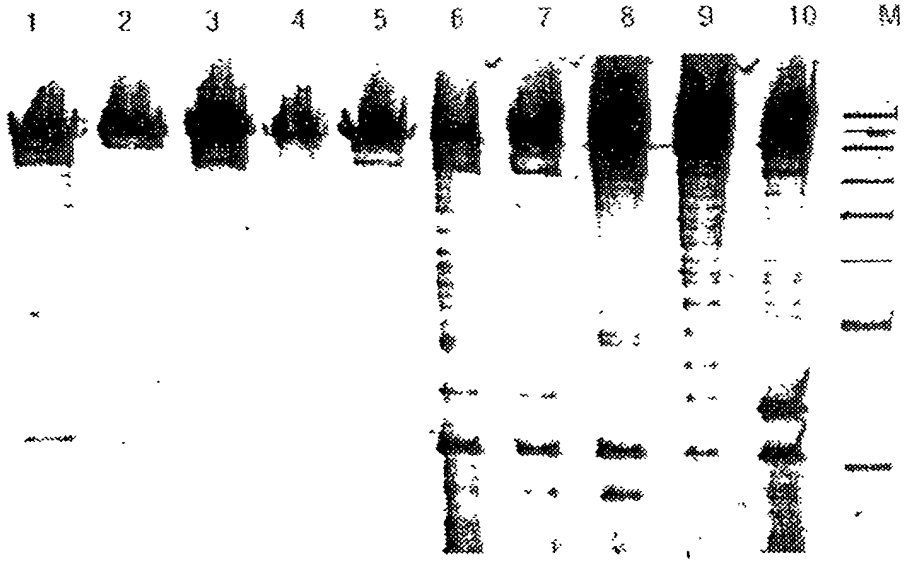


FIG. 91B

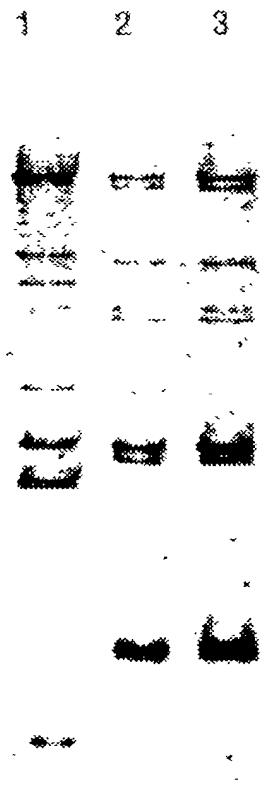


FIG. 92

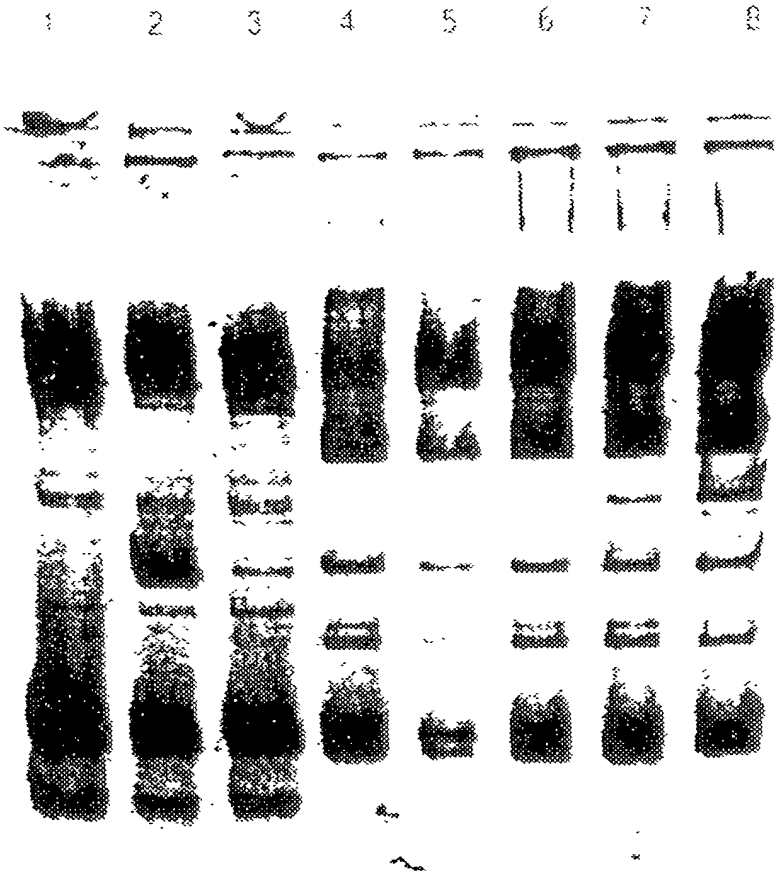


FIG. 93

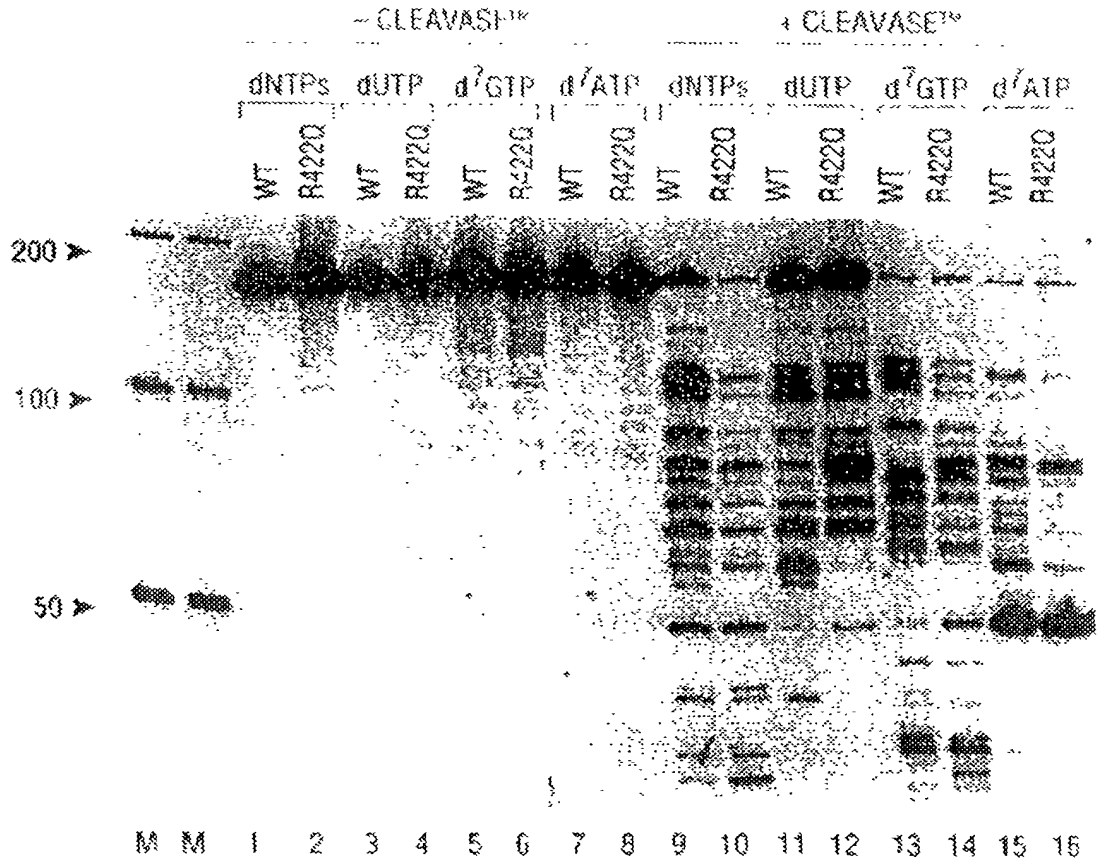

CLEAVASE
CLEAVASE
dNTPs
dUTP
d7GTP
d7ATP
dNTPs
dUTP
d7GTP
d7ATP
WT
R422Q
200
100
50
M M 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

FIG. 94